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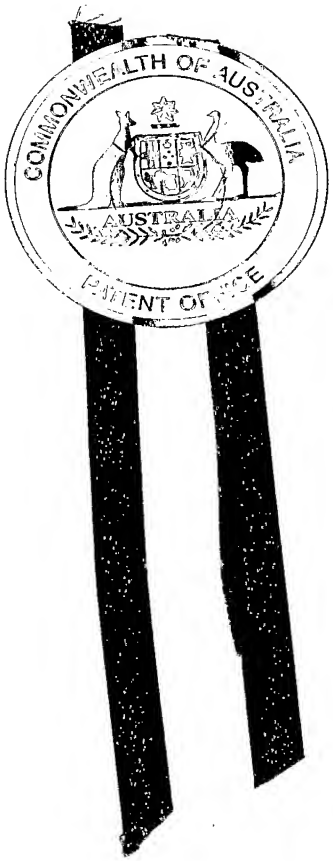

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Eleventh day of April 2005

JANENE PEISKER
TEAM LEADER EXAMINATION
SUPPORT AND SALES

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Applicant(s):

THE UNIVERSITY OF SYDNEY

Invention Title:

COPPER COMPLEXES

The invention is described in the following statement:

COPPER COMPLEXES

FIELD OF THE INVENTION

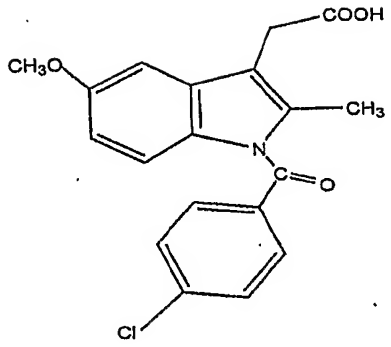
The present invention relates to copper complexes containing ligands having anti-inflammatory activity, including copper complexes of indomethacin. The invention also relates to the use of the complexes in the treatment of inflammatory conditions in humans and animals.

BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat a variety of inflammatory conditions in humans and animals. NSAIDs are, for example, used to treat inflammatory conditions such as rheumatoid arthritis, osteoarthritis, acute musculoskeletal disorders (such as tendonitis, sprains and strains), lower back pain (commonly referred to as lumbago), and inflammation, pain and edema following surgical or non-surgical procedures. However, many NSAIDs cause adverse effects in humans and animals, particularly adverse gastrointestinal effects.

Indomethacin is a NSAID and is effective in treating inflammatory conditions in humans and animals. However, indomethacin can cause severe adverse gastrointestinal effects in humans and animals, particularly when administered orally. In humans, oral administration of indomethacin can cause ulcerations in the oesophagus, stomach, duodenum and intestines, and some fatalities have been reported. In dogs, indomethacin causes fatal gastrointestinal haemorrhaging. Adverse effects associated with the topical administration of indomethacin have been reported in "Anti-inflammatory activity of Indomethacin following topical application", Amico-Roxas, M.; Matera, M.; Caruso, A.; Puglisi, G.; Bernardini, R.; Rinaldo, G. Rivista Europea per le Scienze Mediche e Farmacologiche (1982), 4(2), 199-204. Adverse gastrointestinal effects have also been reported for administration of indomethacin by suppository. The adverse effects of indomethacin have limited the use of indomethacin in the treatment of inflammatory conditions in humans and animals.

Indomethacin has the structure:



In indomethacin, the benzene ring has a chloro substituent at the 3-position. Similar compounds in which the benzene ring is substituted at the 3-position with a halo substituent other than Cl, the benzene ring is substituted with a halo substituent at a position other than the 3-position, and/or the benzene ring has two or more halo substituents, also have similar anti-inflammatory activity to indomethacin (Loll, P. J.; Picot, D.; Ekabo, O.; Garavito, R. M. *Biochemistry* **1996**, *35*, 7330-7340; Touhey, S.; O'Connor, R.; Plunkett, S.; Maguire, A.; Clynes, M. *Eur. J. Cancer* **2002**, *38*, 1661-1670; Fukaya, C.; Naito, Y.; Hanada, S.; Watanabe, M.; Yokoyama, K. Preparation of fluorinated indoleacetic acid derivatives as antiinflammatory drugs. U.S. (1989), 6 pp. Cont.-in-part of U.S. Ser. No. 788,445, abandoned). Some of these compounds show selectivity for inhibition of the COX-II enzyme relative to the COX-I enzyme, and cause less gastrointestinal toxicity than indomethacin (Weder, J. E.; Dillon, C. T.; Hambley, T. W.; Kennedy, B. J.; Lay, P. A.; Biffin, J. R.; Regtop, H. L.; Davies, N. M. *Coord. Chem. Rev.* **2002**, *232*, 95-126). Other compounds having a similar structure to indomethacin and having anti-inflammatory activity are described in WO2005/002525.

It has been found that dinuclear metal complexes of indomethacin (containing two metal coordination centres) cause less adverse side effects, and result in increased uptake of the drug, compared to free indomethacin.

For example, the oral administration of the dinuclear Cu(II) complex of indomethacin, bis(*N*,*N*-dimethylformamide)tetrakis-μ-(*O*,*O'*-Indo)dicopper(II) complex ([Cu_2(Indo)$_4$(DMF)$_2$]), has been found to cause less gastrointestinal toxicity than indomethacin; and it has been claimed that the complex has increased anti-inflammatory activity compared to indomethacin. The mechanism of the reduced gastrointestinal toxicity has not been elucidated. However, it is believed that it is at least in part due to the complex being more lipophilic than indomethacin, which leads to greater absorption of the complex.

Compositions containing this complex, sold under the name Cu-Algesic, have been used in veterinary practice in Australia, New Zealand, South Africa and other countries. These compositions are in the form of a tablet or a paste.

All the metal complexes of indomethacin described to date as having reduced gastrointestinal toxicity compared to indomethacin are dinuclear metal complexes. Recently the first mononuclear indomethacin complex, [Cu(Indo)$_2$(Py)$_3$], was prepared and a preliminary X-ray structure was reported in which both of the indomethacin ligands were monodentate (Preparation and Characterization of Dinuclear Copper-Indomethacin Anti-Inflammatory Drugs. Morgan, Y. R.; Turner, P.; Kennedy, B. J.; Hambley, T. W.; Lay, P. A.; Biffin, J. R.; Regtop, H. L; Warwick, B. *Inorg. Chim. Acta* **2001**, *324*, 150-161). While no information on gastrointestinal toxicity has been reported for this mononuclear complex, mononuclear Zn(II)-Indo complexes have been found to have greater gastrointestinal toxicity than the Zn(II)-Indo dimers (Zhou, Q., PhD Thesis, University of Sydney, 2001).

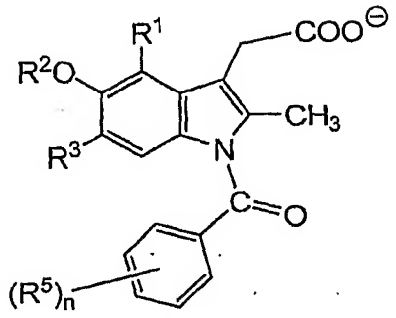
It would be advantageous to provide novel metal complexes of indomethacin and similar anti-inflammatory compounds that cause less adverse gastrointestinal effects than the free compound.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a complex of the formula (1):

$[Cu(\eta^2\text{-}L^1)_2L_2]^p$ (1)

wherein "η^2-L^1" is a bidentate ligand of the formula L^1:

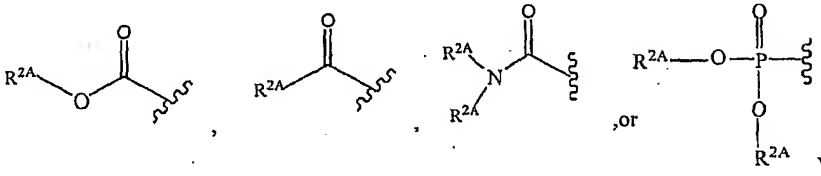


(L^1)

wherein:

R^1 is H or halo (i.e., Cl, F, Br or I);

R^2 is H; a C_1 to C_6 alkyl, an alkenyl or an alkynyl, where the C_1 to C_6 alkyl, alkenyl or alkynyl may be optionally substituted; or



wherein each R^{2A} is independently selected from the group consisting of H, C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl and arylalkyl, where the C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl or arylalkyl may be optionally substituted;

R^3 is H or halo;

each R^5 is independently selected from the group consisting of halo, $-CH_3$, -CN, $-OCH_3$, $-SCH_3$ and $-CH_2CH_3$, where the $-CH_3$, $-OCH_3$, $-SCH_3$ or $-CH_2CH_3$ may be optionally substituted; and

n is 1, 2, 3, 4 or 5;

each L is independently selected and is a monodentate ligand,

and p is the charge of the complex.

When R^2 is a C_1 to C_6 alkyl, an alkenyl or an alkynyl, the C_1 to C_6 alkyl, alkenyl or alkynyl may be substituted with one or more substituents. The one or more

substituents may, for example, be independently selected from the group consisting of halo, -OH, -COOH and $-NH_2$.

When R^{2A} is a C_1 to C_6 alkyl, an alkenyl, an alkynyl, an aryl, a cycloalkyl or an arylalkyl, the C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl or arylalkyl may be substituted with one or more substituents. The one or more substituents may, for example, be independently selected from the group consisting of halo, –OH, -COOH and $-NH_2$.

When R^5 is $-CH_3$, $-OCH_3$ $-SCH_3$ or $-CH_2CH_3$, the $-CH_3$, $-OCH_3$, $-SCH_3$ or $-CH_2CH_3$ may be substituted with one or more substituents. The one or more substituents may, for example, be independently selected from the group consisting of halo, -OH, -COOH and $-NH_2$.

R^1 is typically H.

R^3 is typically H.

R^2 is typically CH_3.

Each R^5 is typically halo (i.e. F, Cl, Br or I), and n is typically 1, 2 or 3.

L^1 may for example be Indo.

The present inventors have surprisingly found that complexes of formula (1) cause less adverse gastrointestinal effects (particularly less adverse effects in the small intestines) than an equimolar dose of the group of the formula L^1 in the form of the free compound L^1H (where L^1 is as defined above). The present inventors have also found that complexes of formula (1) cause less adverse gastrointestinal effects than, or similar adverse gastrointestinal effects to, an equimolar dose of L^1 in the form of a dinuclear copper complex containing the ligand L^1 as a bridging ligand. The lower or similar gastrointestinal toxicity of the mononuclear complexes of formula (1) compared to dinuclear complexes is different to what was observed for zinc-

indomethacin complexes (Dillon, C. T.; Hambley, T. W.; Kennedy, B. J.; Lay, P. A.; Zhou, Q.; Davies, N. M.; Biffin, J. R.; Regtop, H. L. *Chem. Res. Toxicol.*, **2003**, *16*, 28-37). The present inventors have further found that complexes of formula (1) cause surprisingly less adverse gastrointestinal effects (particularly less adverse effects in the small intestines) than an equimolar dose of L^1 in the form of a mononuclear copper-indomethacin complex containing one or more monodentate ligands of the formula L^1.

In a second aspect, the present invention provides a pharmaceutical composition comprising a complex according to the first aspect of the present invention and a pharmaceutically acceptable carrier. The composition may be suitable for administration by oral administration, topical application, as a suppository, by inhalation or by some other route.

In a third aspect, the present invention provides a method of treating an inflammatory condition in a human or animal, the method comprising administrating to the human or animal a therapeutically effective amount of a complex according to the first aspect of the present invention. The animal may, for example, be a dog, a cat, a cow, a horse, a camel, etc. The complex may be administered orally, topically, by injection, by suppository, by inhalation or by some other route.

In a fourth aspect, the present invention provides the use of a complex of formula (1) in the manufacture of a medicament for the treatment of an inflammatory condition.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is the UV-Vis solution spectra of: (a) $[Cu_2(Indo)_4(DMA)_2]$ (0.113 and 1.133 mg/mL in DMA); (b) $[Cu(Indo)_2(Pyrro)_2]$ (0.1062 and 1.062 mg/mL in pyrrolidine); (c) $[Cu_2(Indo)_4(THF)_2]$ (0.106 and 1.016 mg/mL in THF); (d) $[Cu_2(Indo)_4(ACN)_2]$ (0.01036 and 1.036 mg/mL in ACN); (e) $[Cu(Indo)_2(Py)_3]$ (0.1045 and 1.045 mg/mL in Py) and (f) IndoH (0.0132 mg/mL in DMF). The loss of intensity of the absorbance in the UV region in some solvents was due to the absorbance of the solvent.

Figure 2 is the IR spectra of: (a) $[Cu(Indo)_2(Py)_3]$; (b) $[Cu(Indo)_2(Pyrro)_2]$; (c) $[Cu_2(Indo)_4(ACN)_2]$; (d) $[Cu_2(Indo)_4(THF)_2]$; (e) $[Cu_2(Indo)_4(DMA)_2]$; (f) $[Cu_2(OAc)_4(OH_2)_2]$; and (g) IndoH in a KBr matrix.

Figure 3 is the X-band EPR spectra at room-temperature of (a) $[Cu(Indo)_2(Py)_3]$ in pyridine solution; and of powders of (b) $[Cu(Indo)_2(Py)_3]$; (c) $[Cu(Indo)_2(Pyrro)_2]$; (d) $[Cu_2(Indo)_4(ACN)_2]$; (e) $[Cu_2(Indo)_4(THF)_2]$; and (f) $[Cu_2(Indo)_4(DMA)_2]$.

Figure 4 is the X-ray powder diffraction patterns of (a) dinuclear $[Cu_2(Indo)_4L_2]$ (L = DMA, THF or ACN); and (b) mononuclear $[Cu(Indo)_2(Py)_3]$ complexes. The short vertical marks show the positions of the Bragg reflections expected from the results of all the single-crystal analyses. There is no reflection for $[Cu_2(Indo)_4(ACN)_2]$.

Figure 5 is a series of graphs of the bond distances and Cu displacement in dinuclear complexes of the formula $[Cu_2(Indo)_4L_2]$ (L = THF, DMF, DMA, DMSO or Py).

Figure 6 is the ORTEP[39] depiction of the mononuclear complex $[Cu(Indo)_2(Py)_3]$ with atomic displacement parameters at the 20% level (150 K).

Figure 7 is the ORTEP[39] depiction of the mononuclear complex $[Cu(Indo)_2(Pyrro)_2]$ with atomic displacement parameters at the 20% level.

Figure 8 is two graphs of the macroscopic gastrointestinal ulcerations observed in rats following oral administration with: (a) 2% (w/v) CMC solution (control); (b) IndoH (10 mg/kg); (c) Cu-acetate; and equimolar Indo and Cu doses of (d) physical mixture of Cu-acetate & IndoH; (e) $[Cu_2(Indo)_4(DMF)_2]$; (f) $[Cu(Indo)_2(Py)_3]$; and (g) $[Cu(Indo)_2(Pyrro)_2]$ in CMC solution in **(1)** the stomach and **(2)** the small intestine. Each bar represents the mean ± SEM for 4–18 rats.

Figure 9 is a graph of the effect on carrageenan-induced paw edema of oral administrated: (a) 2% (w/v) CMC solution (control); (b) IndoH (10 mg/kg); (c) Cu-acetate; and equimolar Indo and Cu doses of: (d) physical mixture of Cu-acetate &

IndoH; (e) $[Cu_2(Indo)_4(DMF)_2]$; (f) $[Cu(Indo)_2(Py)_3]$; and (g) $[Cu(Indo)_2(Pyrro)_2]$; in 2% (w/v) CMC solution. Each bar represents the mean ± SEM for 3–11 rats.

DETAILED DESCRIPTION OF THE INVENTION

In this specification, the abbreviation "IndoH" refers to the uncharged form of indomethacin, and the abbreviation "Indo" refers to the deprotonated anionic form.

In this specification, the abbreviation "ACN" refers to acetonitrile, "THF" refers to tetrahydrofuran, "Py" refers to pyridine, "Pyrro" refers to pyrrolidine, "DMA" refers to *N,N*-dimethylacetamide, "DMSO" refers to dimethylsulfoxide, and "DMF" refers to *N,N*-dimethylformamide.

In this specification, the term "halo" refers to fluoro, chloro, bromo or iodo.

In this specification, the term "alkyl" used either alone or in a compound word such as "arylalkyl", refers to a straight chain, branched or mono- or poly-cyclic alkyl. Examples of straight chain and branched alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, and 1,1,2-trimethylpropyl. Examples of cyclic alkyl include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In this specification, the term "cycloalkyl" refers to a saturated monocyclic or poly-cyclic alkyl having 3 to 12 carbons.

In this specification, the term "alkenyl" refers to a straight chain, branched or cyclic alkenyl. Preferably the alkenyl is a C_2 to C_{20} alkenyl, more preferably C_2 to C_6 alkenyl. Examples of alkenyl include vinyl, allyl, 1-methylvinyl, butenyl, isobutenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methylcyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-

cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

In this specification, the term "alkynyl" refers to a radical of a straight chain, branched or cyclic alkynyl, preferably a C_2 to C_{20} alkynyl, more preferably a C_2 to C_6 alkynyl.

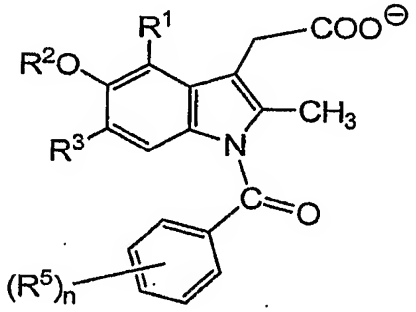
In this specification, the term "aryl" used either alone or in compound words such as "arylalkyl", refers to a radical of a single, polynuclear, conjugated or fused aromatic hydrocarbon or aromatic heterocyclic ring system. Examples of aryl include phenyl, naphthyl and furyl. When the aryl comprises a heterocyclic aromatic ring system, the aromatic heterocyclic ring system may contain 1 to 4 heteroatoms independently selected from N, O and S and up to 9 carbon atoms in the ring.

In this specification the term "arylalkyl" refers to an alkyl substituted with an aryl group. An example of arylalkyl is benzyl.

The present invention relates to complexes of the formula (1):

$$[Cu(\eta^2\text{-}L^1)_2L_2]^p \qquad (1)$$

wherein "η^2-L^1" is a bidentate ligand of the formula L^1:

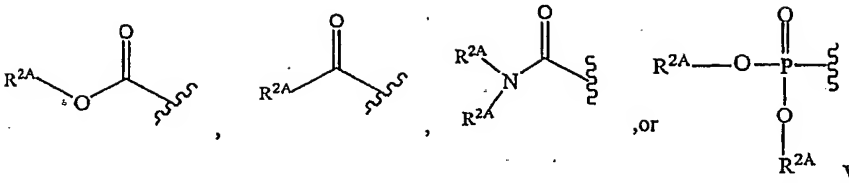


(L^1)

wherein:

R^1 is H or halo (i.e., Cl, F, Br or I);

R^2 is H; a C_1 to C_6 alkyl, an alkenyl or an alkynyl, where the C_1 to C_6 alkyl, alkenyl or alkynyl may be optionally substituted; or



wherein each R^{2A} is independently selected from the group consisting of H, C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl and arylalkyl, where the C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl or arylalkyl may be optionally substituted;

R^3 is H or halo;

each R^5 is independently selected from the group consisting of halo, $-CH_3$, -CN, $-OCH_3$, $-SCH_3$ and $-CH_2CH_3$, where the $-CH_3$, $-OCH_3$, $-SCH_3$ or $-CH_2CH_3$ may be optionally substituted; and

n is 1, 2, 3, 4 or 5;

each L is independently selected and is a monodentate ligand,

and p is the charge of the complex.

As used in this specification including the claims, by a "bidentate ligand" it is meant a ligand having two co-ordination bonds to a metal atom. Bidentate ligands include unsymmetric bidentate ligands with one weaker and one relatively stronger bond to the metal atom. By a "monodentate ligand" it is meant a ligand having a single co-ordination bond with a metal atom.

When R^2 is a C_1 to C_6 alkyl, an alkenyl or an alkynyl, the C_1 to C_6 alkyl, alkenyl or alkynyl may be substituted with one or more substituents. The one or more substituents may, for example, be independently selected from the group consisting of halo, -OH, -COOH and $-NH_2$.

When R^{2A} is a C_1 to C_6 alkyl, an alkenyl, an alkynyl, an aryl, a cycloalkyl or an arylalkyl, the C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl or arylalkyl may be substituted with one or more substituents. The one or more substituents may, for example, be independently selected from the group consisting of halo, –OH, -COOH and $-NH_2$.

When R^5 is $-CH_3$, $-OCH_3$, $-SCH_3$ or $-CH_2CH_3$, the $-CH_3$, $-OCH_3$, $-SCH_3$ or $-CH_2CH_3$

may be substituted with one or more substituents. The one or more substituents may, for example, be independently selected from the group consisting of halo, -OH, –COOH and $–NH_2$.

Typically n is 1, 2 or 3, and each R^5 is independently selected from I, Br, Cl, or F. In some embodiments, n is 1, 2 or 3 and each R^5 is independently selected from Cl and Br.

L^1 may be Indo.

L may be any monodentate ligand. For a complex to be administered to a human or animal, L is preferably a pharmaceutically acceptable ligand. By a "pharmaceutically acceptable ligand" it is meant a ligand that does not cause any or a substantial adverse reaction when the complex is administered to a human or animal patient.

However, complexes of the formula (1) where one or more L is not a pharmaceutically acceptable ligand fall within the scope of the present invention. Such complexes may be used, for example, as an intermediate in the preparation of complexes of formula (1) where each L is a pharmaceutically acceptable ligand.

L may be a charged or uncharged monodentate ligand. When each L is a neutral ligand, the complex of formula (1) is neutral in charge (i.e., p is 0). However, if L is an anionic ligand, the complex of formula (1) will be charged. In some embodiments, p is 1– or 2–.

The complex of formula (1) may be in solution, or may be in the form of a solid. Crystals of a complex of formula (1) may include solvents of crystallisation, and crystals of a complex of formula (1) incorporating solvents of crystallisation fall within the scope of the present invention. Crystals of a complex of formula (1) may also include waters of crystallisation. Water molecules are present as an impurity in all non-aqueous solvents. Crystals of a complex of formula (1) including waters of crystallisation fall within the scope of the prevent invention.

If L is an anionic ligand, a solid of the complex of formula (1) will include cations that are counterions to the anionic complexes. Such solids, include solids having the following formulae:

$Y[Cu(\eta^2\text{-}L^1)_2L_2]$ (1a)

and

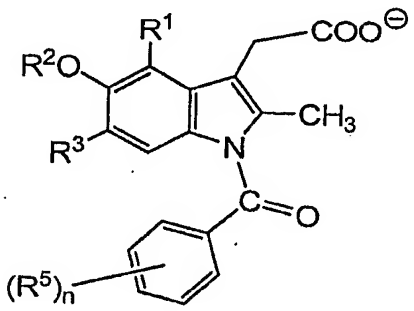
$Y'_2[Cu(\eta^2\text{-}L^1)_2L_2]$ (1b)

wherein η^2-L^1 and L are as defined above for formula (1), Y is a counterion having a 2+ charge and Y' is a counterion having a 1+ charge.

The present inventors have found that complexes of formula (1) cause less adverse gastrointestinal effects than the administration of an equimolar amount of the group of the formula L^1 in the form of the free compound L^1H. The inventors have also found that complexes of formula (1) cause less adverse gastrointestinal effects than the administration of an equimolar amount of L^1 in the form of a mononuclear copper complex containing one or more monodentate ligands of formula L^1. Mononuclear copper complexes with one or more monodentate ligands of formula L^1 include complexes of the formula (2):

$[Cu(\eta^1\text{-}L^1)_mL_q]^p$ (2)

wherein "η^1-L^1" is a monodentate ligand of the formula L^1:

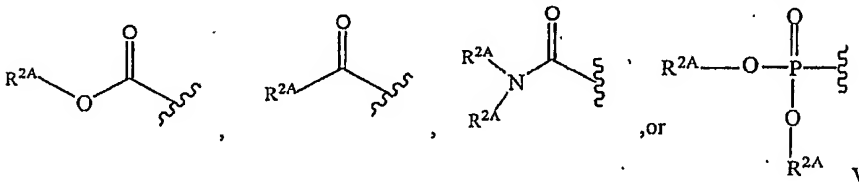


(L^I)

wherein:

R^1 is H or halo (i.e., Cl, F, Br or I);

R^2 is H; a C_1 to C_6 alkyl, an alkenyl or an alkynyl, where the C_1 to C_6 alkyl, alkenyl or alkynyl may be optionally substituted (for example, with one or more substituents independently selected from the group consisting of halo, -OH, -COOH and $-NH_2$); or



wherein each R^{2A} is independently selected from the group consisting of H, C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl and arylalkyl, where the C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl or arylalkyl may be optionally substituted (for example, with one or more substituents independently selected from the group consisting of halo, –OH, -COOH and $-NH_2$);

R^3 is H or halo;

each R^5 is independently selected from the group consisting of halo, $-CH_3$, -CN, $-OCH_3$, $-SCH_3$ and $-CH_2CH_3$, where the $-CH_3$, $-OCH_3$, $-SCH_3$ or $-CH_2CH_3$ may be optionally substituted (for example, with one or more substituents independently selected from the group consisting of halo, -OH, -COOH and $-NH_2$); and

n is 1, 2, 3, 4 or 5;

each L is independently selected and is a monodentate ligand or polydentate ligand, m is an integer from 1 to 6, q is 0 or an integer from 1 to 5, and p is the charge of the complex. When each L is a monodentate ligand, m+q = 4, 5 or 6. Complexes of formula (2) include the complex $[Cu(\eta^1\text{-Indo})_2(Py)_3]$ where "Py" is pyridine.

The present inventors have found that the oral administration of a complex of formula (1) causes less adverse gastrointestinal effects than the oral administration of an equimolar amount of the ligand L^1 in the form of a complex of the formula (2).

The present inventors have found that the adverse gastrointestinal effects associated with some metal complexes of indomethacin are caused at least in part by the release of some of the indomethacin from the complex. Metal complexes of indomethacin are typically administered to patients in the form of a pharmaceutical composition containing the complex. Indomethacin may be released from the complex during the manufacture of the pharmaceutical composition, during storage of the pharmaceutical

composition, or after the complex is administered to the human or animal patient. The present inventors have found that the ligand L^1 is more tightly bound in complexes of formula (1) than in complexes of formula (2), and thus the ligand L^1 is less readily released from a complex of formula (1) compared to complexes of formula (2). The present inventors have found that the oral administration of complexes of formula (2) is associated with similar gastrointestinal side effects to the oral administration of an equimolar dose of L^1 in the form of the free compound L^1H.

The present inventors found that complexes of formula (1) are formed when copper(II) indomethacin complexes are formed using strong donor ligands.

Complexes of formula (1) may for example be formed using the ligand pyrrolidine. Other ligands having a similar donor strength to, or a greater donor strength than, pyrrolidine can also form complexes of formula (1). In some embodiments, L is a ligand containing an *N*-heterocyclic group. Ligands containing an *N*–heterocyclic group include pyrrolidine, alkyl-substituted pyrrolidines, proline, proline derivatives, imidazole, imidazole derivatives such as substituted imidazoles or ligands containing an imidazole ring (e.g. benzimidazole), pyrrole, ligands containing pyrrole, nicotinamides and nicotinic acids. In some embodiments, L is an amine, eg NH_3 or an organic amine (e.g. diethylamine), an alcohol or an amide (e.g. diethylacetamide), or another ligand that is a strong donor such as triethylphosphate.

L may be a solvent having a solvent donor number of about 30 or greater.

Complexes of formula (1) may, for example, be prepared by direct reaction of the appropriate ratios of a compound of the formula L^1H where L^1 is as defined above and a copper salt such as copper(II) acetate in a solvent having a solvent donor number of about 30 or greater, the solvent forming the ligand L in the resulting complex. Complexes of formula (1) may also be prepared by adding a solvent having a solvent donor number of about 30 or greater, or adding a ligand that is not a solvent but has a similar donor strength to a solvent having a solvent donor number of about 30 or greater, to a solution of Cu(II) and L^1 in a weaker donor solvent.

Alternatively, complexes of formula (1) can be prepared by re-crystallisation of a dinuclear complex, such as $[Cu_2(Indo)_4(DMF)_2]$, in a solvent having a solvent donor number of about 30 or greater, such as pyrrolidine, or in a solvent containing a ligand that is a strong donor.

The composition of the present invention comprises a complex of formula (1) together with a pharmaceutically acceptable carrier. As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the complex to a human or animal. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. The carrier is "pharmaceutically acceptable" in the sense of being not biologically or otherwise undesirable, i.e., the carrier may be administered to a human or animal along with the complex without the carrier causing any or a substantial adverse reaction.

The complexes of formula (1) are more lipophilic than compounds of the formula L^1H and thus are more easily absorbed through membranes and taken up by tissues locally. The complexes of formula (1) are, therefore, expected to be more readily absorbed than compounds of the formula L^1H when administered topically.

Compositions of the present invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), ophthalmological, vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The composition may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. Such methods include the step of bringing into association the complex with the carrier. Typically the carrier consists of two or more ingredients. In general, the composition of the present invention is prepared by uniformly and intimately bringing into association the complex with the carrier, and then if necessary shaping the product. Typically, the complex and the one or more ingredients making up the carrier may be mixed in any order.

A composition of the present invention for oral administration may be in the form of a viscous paste, a tablet, a capsule, a chewable composition, or any other form suitable

for oral administration. If desired, the composition may be encapsulated in a soft or hard capsule by techniques known in the art.

Compositions for oral administration include, for example, a composition containing 2% (w/v) of a complex of formula (1) in CMC solution. Another example of a composition for oral administration is a paste formulation comprising 2% (w/v) of a complex formula (1), one or more glycofurols (e.g. tetraglycol), one or more surfactants, one or more thickeners and a medium chain triglyceride.

A composition for oral use may comprise one or more agents selected from the group of sweetening agents, disintegrates, lubricants, flavouring agents, colouring agents and preserving agents in order to produce a pharmaceutically elegant and palatable preparation.

A chewable composition may for example comprise the complex of formula (1), one or more flavours, a base formulation, one or more preservatives, one or more pH modifiers, one or more desiccants and one or more fillers. For a chewable composition for horses, the base may comprise pre-gel starch, gelatine, flour and water. For example, a chewable composition for horses may comprise the complex of formula (1), flavour, the base (comprising pre-gel starch, gelatine, flour and water), and other components including phosphoric acid, salt, sugar, sorbitol and/or glycerol, sorbic acid and/or potassium sorbate, benzoic acid, propionic acid and maltodextrin. A chewable composition for dogs may comprise the complex of formula (1), meat emulsion, an acidulate (e.g. phosphoric acid), one or more antifungal agents (e.g. benzoic acid and sorbic acid), sugar or sugar alcohol, and salt.

A composition of the present invention for topical application may comprise the complex of formula (1) in a conventional oil-in-water emulsion, water-in-oil emulsion, or water-immiscible pharmaceutical carrier suitable for topical application. Such carriers include for example, lacrilube, cetomacrogol cream BP, wool fat ointment BP or emulsifying ointment BP. Such carriers are in the form of an emulsion or are immiscible with water.

An example of a composition for topical application is a composition comprising 0.5-2% w/w of the complex of formula (1) in an emulsifying cream; the emulsifying cream consisting of:

cetomacrogol emulsifying wax	15 g
liquid paraffin	10 g
white soft paraffin	10 g
chlorocresol	0.1 g
propylene glycol	5 ml
purified and cooled water	to 100 g.

Chlorocresol (4-chloro-3-methylphenol) is a preservative.

Another example of a topical composition is a composition consisting of 0.5-2% w/w of the complex of formula (1) in wool fat. This composition is immiscible with water.

Compositions for parenteral administration include compositions in the form of sterile aqueous or non-aqueous suspensions and emulsions.

Typically, the complex of formula (1) constitutes about 0.1 to about 20% by weight of the composition.

In some embodiments, the composition of the present invention does not comprise any therapeutically active ingredients in addition to the complex of formula (1). In other embodiments, the composition of the present invention may include one or more therapeutically active agents in addition to the complex of formula (1).

In some embodiments, all of the groups of the formula L^1 present in the composition are present as part of a complex of formula (1). In other embodiments, some groups of the formula L^1 present in the composition are present in some other form, e.g. in the form of the free compound L^1H, in the form of the ion L^1, as part of a dimer complex containing the ligand L^1 or as part of a complex of formula (2). In such embodiments, typically more than 50%, more typically more than 80%, and even

more typically more than 95%, of groups of the formula L^1 present in the composition are present as part of a complex of formula (1).

The present invention also provides a method for treating an inflammatory condition in a human or animal, the method comprising administering to the human or animal a therapeutically effective amount of a complex according to the first aspect of the present invention. The complex is typically administered to the human or animal by administering a composition containing the complex. The complex may be administered orally, topically, by injection, by suppository, by inhalation or by some other route, depending on the inflammatory condition to be treated.

The human or animal may be any human or animal having a disease or condition that requires treatment with a complex of the present invention. The animal is typically a mammal, and may be a non-human primate or non-primate. The mammal may for example be a companion animal such as a dog or cat, or a domestic animal such as a horse, pony, donkey, mule, camel, llama, alpaca, pig, cow or sheep, or a zoo animal.

Suitable mammals include members of the Orders *Primates, Rodentia, Lagomorpha, Cetacea, Carnivora, Perissodactyla* and *Artiodactyla.*

The inflammatory condition may for example be rheumatoid arthritis, osteoarthritis, acute musculoskeletal disorders (such as tendonitis, sprains and strains), or lower back pain (commonly referred to as lumbago). The inflammatory condition may also be inflammation, pain or edema following surgical or non-surgical procedures.

As used herein, the term "therapeutically effective amount" means an amount effective to yield a desired therapeutic response, for example, to treat an inflammatory condition. The specific "therapeutically effective amount" will vary with such factors as the particular condition being treated, the physical condition of the human or animal, the type of animal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific composition employed. The dosage administered and route of administration will be at the discretion of the attending clinician or veterinarian.

The invention is described below by reference to the following non-limiting examples. It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as described in the following Examples without departing from the spirit or scope of the invention as broadly described. The Examples are, therefore, to be considered in all respects as illustrative and not restrictive.

EXAMPLES

Example 1 – Preparation of *bis(η^1-O-Indo)tris(pyridine)copper(II), [Cu(Indo)$_2$(Py)$_3$]* ("Complex 1") and *bis(η^2-O,O'-Indo)bis(pyrrolidine)copper(II)-2-pyrrolidine monohydrate, [Cu(Indo)$_2$(Pyrro)$_2$]·2Pyrro·H$_2$O* ("Complex 2").

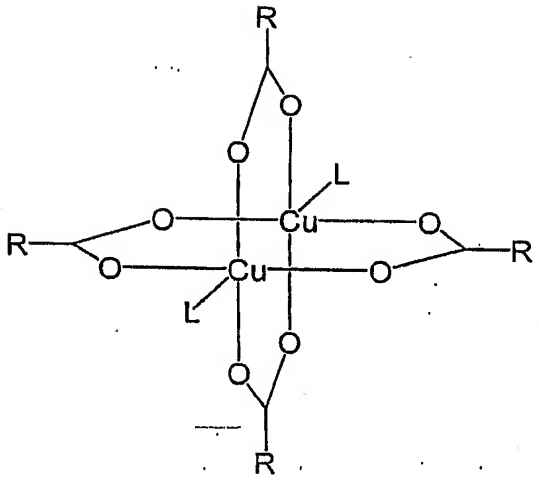
Experimental

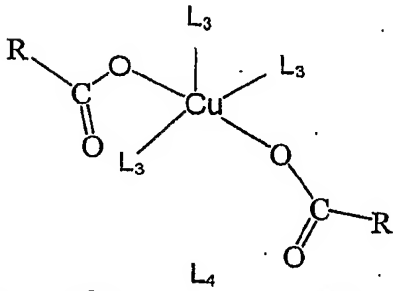
Chemicals

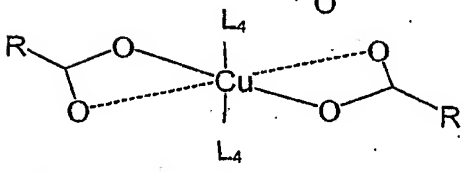
IndoH of pharmaceutical grade (Sigma-Aldrich) was used as received. $[Cu_2(Indo)_4(DMF)_2]$ was provided by Biochemical Veterinary Research Pty Ltd. (BVR) and was purified by two recrystallisations from DMF. $[Cu_2(OAc)_4(OH_2)_2]$ was obtained from Univar (99% purity). All of the other chemicals were of analytical grade (Sigma-Aldrich).

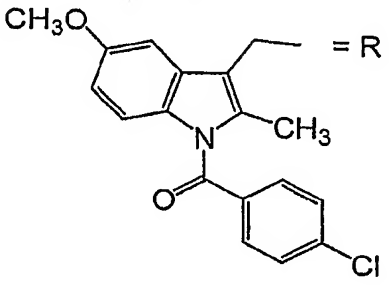
For comparative purposes, the complexes $[Cu_2(Indo)_4(DMA)_2]$, $[Cu_4(Indo)_2(THF)_2]$, $[Cu_2(Indo)_4(ACN)_2]$ and $[Cu_2(Indo)_4(Py)_2]$ were prepared as reported previously (Preparation and Characterization of Dinuclear Copper-Indomethacin Anti-Inflammatory Drugs. Morgan, Y. R.; Turner, P.; Kennedy, B. J.; Hambley, T. W.; Lay, P. A.; Biffin, J. R.; Regtop, H. L; Warwick, B. *Inorg. Chim. Acta* **2001**, *324*, 150-161).

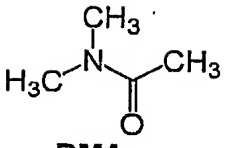
The structures of the Cu-Indo dimers $[Cu_2(Indo)_4(L)_2]$ (where L = DMA, THF, ACN or Py), Complex 1, Complex 2, and their solvent ligands is set out below:







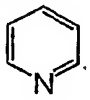


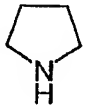
L = 
DMA

L = 
THF

L = $H_3C-C\equiv N$
ACN

L = 
Py

Complex 1 L_3 = 
Py

Complex 2 L_4 = 
Pyrro

1. Bis(η^1-O-Indo)tris(pyridine)copper(II), [Cu(Indo)$_2$(Py)$_3$] (Complex 1).

Crystals of Complex 1 were prepared as reported in Preparation and Characterization of Dinuclear Copper-Indomethacin Anti-Inflammatory Drugs. Morgan, Y. R.; Turner, P.; Kennedy, B. J.; Hambley, T. W.; Lay, P. A.; Biffin, J. R.; Regtop, H. L; Warwick, B. *Inorg. Chim. Acta* **2001**, *324*, 150-161.

Blue tabular crystals were grown by recrystallisation of [Cu_2(Indo)$_4$(DMF)$_2$] twice from mixtures of pyridine and ethanol with 1:1 and 2:5 volume ratios, respectively. *Anal.* Found: C, 62.38; H, 4.67; N, 7.47; Cu, 6.66%. Calc. for $CuC_{53}H_{45}Cl_2N_5O_8$: C, 62.75; H, 4.47; N, 6.91; Cu, 6.26%.

2. Bis(η^2-O,O'-Indo)bis(pyrrolidine)copper(II)-2-pyrrolidine monohydrate, [Cu(Indo)$_2$(Pyrro)$_2$]·2Pyrro·H_2O (Complex 2).

X-ray diffraction quality crystals that consisted of pale blue plates were grown by recrystallisation of [Cu_2(Indo)$_4$(DMF)$_2$] in pyrrolidine as the solvent. *Anal.* Found: C, 59.91; H, 6.32; N, 7.84; Cu, 6.01%. Calc. for $CuC_{54}H_{68}Cl_2N_6O_9$: C, 60.15; H, 6.36; N, 7.80; Cu, 5.84%.

Physical measurements

Elemental microanalyses. Copper analyses were performed with a Varian AA-800 air–acetylene flame atomic absorption spectrophotometer. The C, H, N microanalyses were performed by the Department of Chemistry, University of Otago.

Infrared Spectroscopy. Fourier transform IR spectra were acquired from samples within pressed disks of KBr matrix on a Bio-Rad Win-IR FTS-40 infrared spectrometer (400-4000 cm^{-1}).

UV-Vis Spectroscopy. Diffuse-reflectance solid-state UV-Vis spectra were recorded using a Varian Cary 1E spectrophotometer. UV-Vis spectra of solutions were obtained in 1-cm quartz cells in a Hewlett–Packard 8452A diode-array (190–820 nm)

or a Varian Cary 5E UV-VIS-NIR spectrophotometer. Each complex was dissolved in the same solvent as its solvent ligand.

X-Band Electron Paramagnetic Resonance Spectroscopy. X-band (~9.5 GHz) EPR spectra of powdered and solution samples of the complexes were acquired using a Bruker EMX EPR spectrometer equipped with a standard ER4120 X-band cavity, EMX 035M NMR gaussmeter, EMX 032 field controller, EMX 081 magnet power supply, Bruker EMMX 048T microwave bridge control, and BVT2000 variable temperature unit.

Magnetic Susceptibility. Room-temperature magnetic susceptibilities (χ_g) and magnetic moments (μ_{eff}) were measured with a Sherwood Scientific magnetic susceptibility balance. Iron(II) ammonium sulfate hexahydrate was used as a standard for calibration of the instrument.[6] The value of χ_D was obtained by summing the atomic diamagnetism of all diamagnetic atoms present in $[Cu_2(Indo)_4(L)_2]$, or $[Cu(Indo)_2(L)_3]$ and $[Cu(Indo)_2(L)_2]$ and a small constitutive correction (ε) for specific electronic characteristics, e.g. π-bonds.[6]

X-ray Powder Diffraction. X-ray powder diffraction patterns were collected at room temperature using Cu Kα radiation with a Shimadzu Lab XRD-6000 diffractometer with divergence and anti-scatter slits of 0.5 mm, and receiver and detector slits of 0.15 and 0.6 mm, respectively. These data were collected over the range 5.0–40.0° in steps of 0.02° in 2θ, and a count time per step of 15.0 s. Profiles were fitted using the La-Bail method implemented in the program, Rietica. In these analyses, cell parameters were initially set equal to those reported for $[Cu_2(Indo)_4(DMF)_2]$ and refined using a non-linear least-squares method.

X-ray crystallographic analyses. All structures were obtained from diffraction data collected at low temperatures (150-170 K) on a Bruker SMART 1000 diffractometer equipped with an Oxford Cryosystems Cryostream, using graphite-monochromated Mo Kα radiation generated from a sealed tube. Crystals of Complex 1 and Complex 2

were each attached with Exxon Paratone N, to a short length of fibre supported on a thin piece of Cu wire inserted in a Cu mounting pin.

These crystals were quenched in a cold gas (N_2) stream when mounted on the diffractometer. The SMART 1000 data integration and reduction were performed with SAINT and XPREP,[7] and subsequent computations were performed with TEXSAN.[8] For Complex 1 WINGX,[9] and the XTAL[10] graphical user interface were also used. A Gaussian absorption correction was applied to the data for Complex 1 and Complex 2.[7,11] The structure for Complex 2 was solved in the space group $P\bar{1}$ (#2) by direct methods with SIR97,[12] and extended and refined with SHELXL-97.[13] In all cases, data reduction included the application of Lorentz and polarization corrections.

Cell constants for Complex 1 were obtained from a least-squares refinement against 995 reflections located between 5.35 and 52.34° 2θ. Data were collected at 150(2) K and 295(2) K with ω-scans to 56.48° 2θ. The intensities of 291 standard reflections that were recollected at the end of the experiment did not change significantly during the data collection. The structure was solved in the space group $P2_1/c$(#14) by direct methods with SIR97,[14] and extended and refined with SHELXL-97.[15] The asymmetric unit contains a five-coordinate Cu(II) complex comprised of two indomethacin ligands and three pyridine ligands, together with two pyridine solvent molecules and a water molecule. The water molecule is involved in hydrogen bond interactions between the carboxylate O(2) of one indomethacin ligand, and the O(6) carboxylate oxygen of the second indomethacin ligand. The N(7) pyridine molecule is centred on an inversion site, and is accordingly disordered with N(7) and C(61) sharing the same sites with equal occupancies. In general the non-hydrogen atoms were modelled with anisotropic displacement parameters; isotropic displacement parameters were used for the disordered pyridine solvate molecule. The water hydrogens were located in a final difference map, and a riding atom model was used for all of the hydrogen atoms.

Cell constants for Complex 2 were obtained from a least-squares refinement against 838 reflections located between 5.66 and 52.04° 2θ. Data were collected at 150(2) K with ω-scans to 56.74° 2θ. The intensities of 60 standard reflections recollected at the end of the experiment did not change significantly during the data collection. The

asymmetric unit contains half of a complex molecule with the metal ion located on an inversion site. The non-hydrogen atoms were modelled with anisotropic displacement parameters and in general a riding atom model was used for hydrogen atoms. The pyrrolidine hydrogen site H(2N) was located and the atom was modelled with an isotropic displacement parameter. The complex may be described as a strongly tetragonally distorted octahedral with two equivalent unsymmetric Indo chelate rings (Cu-O(1) is 1.9719(14) Å and Cu-O(2) is 2.5696(16) Å).

Crystallographic data and structure refinement parameters for Complex 1 and Complex 2 in are summarised Table 1.

Results

Synthesis of dinuclear and mononuclear copper complexes

The precipitation of dinuclear $[Cu_2(\mu\text{-Indo})_4(Py)_2]$ or mononuclear $[Cu(\eta^1\text{-Indo})_2(Py)_3]$ is sensitive to both the ratio of ethanol and pyridine and the time taken for recrystallisation (the monomer that initially precipitates slowly dissolves and converts to the less soluble dimer), with the monomeric complex being the dominant species in solution. Elemental analyses of all the Cu(II)-Indo complexes revealed that the resulting complexes contained varying amounts of solvent molecules, which act as ligands bound to the Cu(II), and/or solvents of crystallisation, as is demonstrated by the crystal structural studies and this is expected to be the case for most monomers of both types described herein. The mononuclear Pyrro complex, however, forms exclusively in both the solid-state and solution, with no evidence of a dimer in either state.

UV–Vis spectroscopy

A summary of UV-Vis absorption spectral data for $[Cu_2(Indo)_4L_2]$ (L = DMA, THF or ACN), $[Cu(Indo)_2(Py)_3]$ (Complex 1) and $[Cu(Indo)_2(Pyrro)_2]$ (Complex 2) are given in Table 2. Electronic absorption spectra from solutions of monomers and dimers are given in Fig. 1. Properties of the solvents are listed in Table 3. In Fig. 1, the loss of intensity of the absorbance in the UV region in some solvents was due to the absorbance of the solvent (see Table 3).

The solid-state UV-Vis spectra of both monomer and dimer complexes exhibited a low-energy band centered at about 671 to 728 nm (band I) and more intense higher-energy band at around 345 nm (band II). There are no clear distinctive differences between the dinuclear and mononuclear Cu-Indo complexes in the solid-state UV-Vis spectra.

Table 1. Crystal data and structure refinement parameters for Complex 1 and Complex 2

Complexes	Complex 1	Complex 2
Formula of the Refinement Model	$C_{60\cdot50}H_{50.50}Cl_2CuN_{6.50}O_9$	$C_{46}H_{48}Cl_2CuN_4O_8$
Model Molecular Weight	1151.05	919.32
Crystal color and habit	blue, blade	pale blue, tabular
Crystal system	Monoclinic	Plate
Crystal size (mm)	0.571×0.132×0.036	0.269×0.134×0.032
Space group	$P2_1/c$(#14)	$P\bar{1}$ (#2)
Unit cell dimensions		
a (Å)	13.0694(12)	13.420(4)
b (Å)	44.434(4)	14.845(5)
c (Å)	9.8730(9)	5.3760(17)
α (°)		96.948(5)
β (°)	94.137(2)	91.524(5)

γ (°)		101.892(5)
V (Å^3)	5718.6(9)	1038.9(6)
D_{calc} (g cm^{-3})	1.337	1.469
Z	4	1
λ(Mo Kα) (Å)	0.71073	0.71069
μ (Mo Kα) (mm^{-1})	0.538	0.716
T(GAUSSIAN)$_{min,max}$	0.875, 0.982	0.858, 0.977
$2\theta_{max}$ (°)	56.48	56.74
Index ranges	$-16 \leq h \leq 16$, $-58 \leq k \leq 58$, $-12 \leq l \leq 12$	$-17 \leq h \leq 17$, $-19 \leq k \leq 19$, $-7 \leq l \leq 7$
N	48 866	9421
N_{ind}	12977 (R_{merge} 0.0542)	4745 (R_{merge} 0.0449)
N_{obs}	9014 [$I > 2\sigma$ (I)]	3278 [$I > 2\sigma$ (I)]
N_{var}	701	283
Residuals $R_1(F)$, $wR_2(F^2)$	0.0499, 0.1156 [a,b]	0.0388, 0.0870 [a,c]
Goodness-of-fit on F^2	1.294	0.900
Residual extrema (e Å^{-3})	-0.445, 0.711	–0.274, 0.383

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for $F_o > 2\sigma$ (F_o); $wR2 = (\Sigma w(F_o^2 - F_c^2)^2/\Sigma(wF_c^2)^2)^{1/2}$ all reflections. [b] $w = 1/[\sigma^2(F_o^2) + (0.0400P)^2 + 0.5000P]$, where $P = (F_o^2 + 2F_c^2)/3$. [c] $w = 1/[\sigma^2(F_o^2) + (0.0396P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3$.

Table 2. UV-Vis data of solutions and solid samples (diffuse-reflectance spectra) of Cu-Indo complexes and IndoH.

	Solution	Solid
Compounds	λ_{max} (nm), ε_{max} (M^{-1} cm^{-1})	λ_{max} (nm)
$[Cu_2(Indo)_4(DMA)_2]$	282 s, (354×10^2); 318 sh (225×10^2); 724 s, (405)[a]	341 s, 728 s
$[Cu_2(Indo)_4(THF)_2]$	280 s, (369×10^2); 320 sh (215×10^2); 676 s, (437)[b]	348 s, 728 s
$[Cu_2(Indo)_4(ACN)_2]$	202 s, (181×10^3); 234 sh (863×10^2); 318 sh (285×10^2); 686 s, (570)[c]	345 s, 684 s
$[Cu(Indo)_2(Py)_3]$	322 s, (134×10^2); 658 s, (125)[d]	342 s, 671 s
$[Cu(Indo)_2(Pyrro)_2]$	310 s (105×10^2); 708 s, (153)[e]	
IndoH	270 s, (155×10^2); 318 sh (637×10) [f]	

[a] In DMA. [b] In THF. [c] In ACN. [d] In Py. [e] In Pyrro. [f] In DMF.

Table 3. Some properties of solvents[16,17]

Solvent	ACN	THF	DMA	Py
UV Cutoff (nm)	190	215	268	305
Donor number D_N	14.1	20.0	26.6	33.1

In order to avoid ligand-exchange reactions with the solvent that could lead to structural changes, each Cu-Indo complex was dissolved in the same solvent as that coordinated to the Cu(II) centres for solution spectra. The solution-state UV–Vis spectra of the complexes show a broad absorption band in the visible region around 650–750 nm (Band I). The value of ε for this band in solution is much higher for dinuclear complexes, than for the mononuclear complexes. Similar behaviour is observed with other mononuclear and dinuclear Cu(II) complexes,[1,2,18-23] which suggests that is diagnostic for determining whether the complexes are mononuclear or dinuclear in solution. In addition, there were distinctly different positions of the band

in the visible region for the two different forms of monomers (Table 2 and Figure 1), which appears to be diagnostic of the different structures of the monomers in solution.

Vibrational spectra

The IR spectral data for the complexes $[Cu_2(Indo)_4L_2]$ (L = DMA, THF or ACN), $[Cu(Indo)_2(Py)_3]$ (Complex 1), $[Cu(Indo)_2(Pyrro)_2]$ (Complex 2), $[Cu_2(OAc)_4(OH_2)_2]$ and IndoH are set out in Table 4 and Fig. 2. All of the complexes exhibit characteristic bands for their ligands in the IR spectra. Features of most interest are bands due to the $\nu_{asym}C(=O)_2$, $\nu_{sym}C(=O)_2$, $\nu_{amide}(C=O)$ and ν_{carbo} (–OH) modes. Depending upon the coordination mode of the carboxylate group, i.e., bridging, monodentate or bidentate, the frequency of the $\nu_{sym}C(=O)_2$, stretching vibrations shift to slightly different positions. The IR spectra for all the complexes exhibit an intense absorption band around 1602–1623 cm^{-1} (Table 4), due to the $\nu_{asym}C(=O)_2$ vibrational mode, which is at 1716 cm^{-1} in IndoH. All amide stretching modes $\nu_{amide}(C=O)$ of these complexes and of IndoH produce strong bands near 1685 cm^{-1}. The band due to the $\nu_{sym}C(=O)_2$ stretch is at a lower frequency ~1,400 cm^{-1} in the dimeric species than in the monomeric complexes 1445 and 1437 cm^{-1}, respectively, for complexes 1 and 2. This band is at 1310 cm^{-1} for IndoH. The $\Delta\nu$ values of ca. 200-220 cm^{-1} for carboxylate bridging ligands in dinuclear $[Cu_2(Indo)_4(L)_2]$ complexes, where $\Delta\nu = \nu_{asym}C(=O)_2 - \nu_{sym}C(=O)_2$, are greater than for those for unidentate coordination of the carboxylates in $[Cu(Indo)_2(Py)_3]$ (178 cm^{-1}) and the unsymmetric bidentate coordination in $[Cu(Indo)_2(Pyrro)_2]$ (160 cm^{-1}). These band positions of $\nu_{asym}C(=O)_2$, $\nu_{sym}C(=O)_2$ and the $\Delta\nu$ values are consistent with those observed for $[Cu_2(Indo)_4(DMF)_2]$,[2,16] Zn-Indo analogs[5] and other bridging,[24,29,30] and unidentate[19–21,26] carboxylate complexes of Cu(II). IndoH displays a very broad, intense ν_{carbo} (–OH) stretching absorption in the region of 2500-3300 cm^{-1}. The absence of the ν_{carbo} (–OH) absorption bands of the carboxylic acid in the IR spectra of $[Cu_2(Indo)_4(L)_2]$, $[Cu(Indo)_2(Py)_3]$ and $[Cu(Indo)_2(Pyrro)_2]$ is indicative of carboxylate group binding (Fig. 2).

Table 4. Room-temperature magnetic moment and IR spectral data for the complexes and IndoH

	μ_{eff}[a]	$\nu_{amide(C=O)}$	$\nu_{asym(COO)}$	$\nu_{sym(COO)}$	$\Delta\nu$
Compounds	T = 300.6 K	(cm^{-1})	(cm^{-1})	(cm^{-1})	(cm^{-1})
$[Cu_2(Indo)_4(DMA)_2$	1.48	1685	1602	1404	198
$[Cu_2(Indo)_4(THF)_2]$	1.45	1683	1622	1405	217
$[Cu_2(Indo)_4(ACN)_2]$	1.37	1685	1623	1402	221
$[Cu(Indo)_2(Py)_3]$	1.73	1679	1623	1445	178
$[Cu(Indo)_2(Pyrro)_2]$	—	1684	1597	1437	160
$[Cu_2(OAc)_4(OH_2)_2]$	—	—	1618	1417	201
IndoH	—	1694	1717	1310	407

[a] This is the value per Cu(II) for the dinuclear complexes.

The IR spectral data for $[Cu_2(Ac)_4(OH_2)_2]$ is included in Table 4 for comparison.

Magnetic susceptibility

Room-temperature solid-state effective magnetic moments of the complexes $[Cu_2(Indo)_4L_2]$ (L = DMA, THF or ACN) and $[Cu(Indo)_2(Py)_3]$ (Complex 1) are listed in Table 4. Consistent with anti-ferromagnetic exchange,[31] the room temperature magnetic moments per Cu for the dimers (μ_{eff} =1.37-1.48 B.M) are similar to those observed for $[Cu_2(Indo)_4(DMF)_2]$ and other dinuclear $[Cu_2(RCOO)_4(L)_2]$ complexes[2,25,27,32-36] and are somewhat smaller than that expected for the monomeric Complex 1. These observations are due to the singlet ground state and a thermally populated triplet state,[2,28] the spin interactions occur between the two d^9 Cu(II) ions via the conjugated π-system of the carboxylate bridges.[29] The monomeric Complex 1 has a magnetic moment (μ_{eff} =1.73 B.M) that is typical of a d^9 spin only (no coupling) mononuclear Cu(II), which is consistent with the EPR results.

EPR spectroscopy

The X-band EPR data for various Cu(II)-Indo complexes in solid state and solution are summarized in Table 5. The $[Cu_2(Indo)_4L_2]$ (L = DMA, ACN, THF) complexes exhibited distinctive resonances of the $S = 1$ excited state of the dimeric complexes[1,2] in the X-band EPR spectra (Figure 3). A small resonance at ~ 3300 G in these spectra is due to a trace of a Cu(II) monomer impurity of uncertain structure[2] in the $[Cu_2(Indo)_4L_2]$ complexes. The EPR spectrum of the monomeric complex, $[Cu(Indo)_2(Py)_3]$, at room temperature (Figure 3.a) shows a typical Jahn-Teller distorted axial d^9 spectrum with $g_\parallel > g_\perp$ ($g_\parallel = 2.359$, $g_\perp = 2.074$), which is consistent with a ground state in which the unpaired electron resides in the d_{x2-y2} orbital.[18,21,37,38] The EPR spectrum is distinctly different, however, from that due to $[Cu(Indo)_2(Pyrro)_2]$ ($g_\parallel = 2.266$, $g_\perp = 2.051$) as a result of the different symmetries of the two complexes (Figure 3, Table 5). There is no evidence of contamination with any appreciable amount of the dimer in the EPR spectrum obtained from a powdered sample of the monomeric complex, $[Cu(Indo)_2(Py)_3]$. In pyridine solutions, only signals due to mononuclear species were observed ($g_{eff} = 2.161$), which shows that the dimeric structures were unstable in solutions containing an excess of pyridine. Crystals of mononuclear species could be obtained from these solutions, but they were slowly replaced with time by crystals of the less soluble dimer.

Table 5. X-band EPR Data for Cu(II)-Indo Complexes.

		Dimeric resonance			Monomeric resonance		
Compounds	State	$g_{\parallel}$[a]	$g_{\parallel}$[b]	$g_{\perp}$	$g_{\parallel}$	$g_{\perp}$	g_{eff}[c]
$[Cu_2(Indo)_4(DMA)_2]$	solid	26.45	1.147	1.454	2.334	2.070	2.158
$[Cu_2(Indo)_4(THF)_2]$	solid	25.512	1.147	1.449	2.350	2.071	2.164
$[Cu_2(Indo)_4(ACN)_2]$	solid	31.176	1.139	1.455	2.335	2.077	2.163
$[Cu(Indo)_2(Py)_3]$	solid				2.359	2.074	2.169
$[Cu_2(Indo)_4(Py)_2]$	solution					2.090	2.161
$[Cu(Indo)_2(Py)_3]$	solution					2.090	2.161
$[Cu(Indo)_2(Pyrro)_2]$	solid				2.266	2.051	2.123

[a] This corresponds to H_{z1} in Figure 3. [b] This corresponds to H_{z2} in Figure 3. [c] $g_{eff} = 1/3(g_{\parallel} + 2\, g_{\perp})$, except solution-state taken from spectra.

X-ray Powder Diffraction

X-ray powder diffraction patterns for the dinuclear $[Cu_2(Indo)_4L_2]$ (L = DMA, THF, or ACN) and the mononuclear $[Cu(Indo)_2(Py)_3]$ complexes are shown in Figure 4 and the short vertical marks show the positions of the Bragg reflections expected from the results of all the single-crystal analyses. The derived lattice parameters of $[Cu_2(Indo)_4L_2]$ (L = DMA or THF) and $[Cu(Indo)_2(Py)_3]$ are listed in Table 6, and the patterns can be used to distinguish between monomers and dimers.

Table 6. Lattice Parameters and Selected Details of Refinements of the Powder Diffraction Patterns of $[Cu_2(Indo)_4L_2]$ (L = DMA, THF) and $[Cu(Indo)_2(Py)_3]$ Complexes

Parameters	$[Cu_2(Indo)_4(DMA)_2]$	$[Cu_2(Indo)_4(THF)_2]$	$[Cu(Indo)_2(Py)_3]$
Space group	$P\bar{1}$ (#2)	$P\bar{1}$ (#2)	$P2_1/c$(#14)
a (Å)	11.280(2)	14.493(6)	13.136(7)
b (Å)	13.281(6)	16.896(5)	44.682(2)
c (Å)	16.487(6)	10.046(8)	9.929(1)
α (°)	100.17(2)	106.58(2)	90.00(0)
β (°)	100.61(5)	89.97(0)	94.10(5)
γ (°)	110.94(9)	109.95(2)	90.00(0)

Crystal and molecular structures

Figure 5 shows a comparison of the bond distance and Cu displacement in the complexes $[Cu_2(Indo)_4L_2]$ where L = ACN, THF, DMF, DMA, DMSO or Py. There are no systematic differences in the bonding parameters of these complexes with *O*-donors compared with complexes with the *N*-donor ligands, Py and ACN, except that the Cu–Cu bond was somewhat longer in the Py complex. Fig. 5 summarises the bond distance and Cu displacement from plane for dinuclear $[Cu_2(Indo)_4L_2]$. There are also

no clear trends that distinguish the core geometry of complexes with stronger donor capacity ligands from those with weak donor capacity as the ternary ligand, except there are clear trends in the Cu–Cu distance and the Cu displacement from plane that reflects the donor capacity of the axial ligand, i.e., the Cu–Cu bond weakens as the donor strength of the solvent increases. Thus Fig. 5 demonstrates that increasing the donor strength favours monomer formation over dimer formulation and this has important implications in the preparation of monomeric complexes.

Crystal structure data for $[Cu(Indo)_2(Py)_3]$ were collected at both 150(2) K and 295(2) K. Selected bond lengths and angles for $[Cu(Indo)_2(Py)_3]$ at both temperatures and for $[Cu(Indo)_2(Pyrro)_2]$ are given in Tables 7 and 8. The ORTEP[39] depictions of Complex 1 (with only one orientation of the disordered pyridine molecule shown) and Complex 2 are provided in Figures 6 and 7.

For mononuclear Complex 1, the carboxylate group of Indo is bound as a monodentate ligand and the structure is comprised of a five-coordinate Cu(II) centre with three monodentate pyridine ligands, similar to that reported for another monodentate Cu(II) carboxylate complex that contains the pyridine ligand and having the CuN_3O_2 chromophore.[41] Complex 1 is an essentially five-coordinate square pyramidal Cu centre with the in-plane angular distortion away from the regular square-based pyramidal geometry and with a elongated apical Cu(1)–N(5) bond length of 2.317(2) Å. The two nitrogen atoms N(3) and N(4) and the carboxylate oxygen atoms O(1) and O(5) occupy *trans* positions in the basal plane with basal bond lengths of Cu–N 2.073(2), 2.067(2) Å and Cu–O 1.9635(16), 1.9492(16) Å. The N(3)–Cu(1)–N(4) angle of the basal plane is 166.21(8)°, while the O(5)–Cu(1)–O(1) angle is close to linear, 176.57(7)°.

Complex 2 may be described as a tetragonally distorted octahedron, with a four-coordinate square-planar bonding with weak off axis secondary coordination from the second 'carbonyl' oxygen of the carboxylate, which is bound as an unsymmetric bidentate ligand. The mononuclear Cu bonded in a *trans* square-planar arrangement to two pyrrolidine nitrogen atoms at Cu–N 2.051(2) Å and one short carboxylate oxygen

atoms from each of two Indo ligands at Cu–O(1) 1.9719(14) Å. The remote carboxylate oxygen atoms bind to the Cu atoms Cu···O(2) = 2.5696(16) Å showing weak interactions. The O(1)–Cu(1)–N(2) angle is 93.22(7)°. This structure is comparable to those observed in the X-ray structures of mononuclear Cu(II) carboxylate complexes with the *trans* square-planar CuN_2O_2 ...O_2 chromophore,[21,38,42,43] such as Cu complexes of anti-inflammatory and anti-convulsant drugs, [Cu(aspirinate)$_2$(Py)$_2$] [38] and [Cu(niflumato)$_2$(3-PyMe)$_2$].[43]

Table 7. Selected bond lengths (Å) and bond angles (°) of Complex 1.

Bond lengths	**295(2) K**	**150(2) K**	***Bond angles***	**295(2) K**	**150(2) K**
Cu(1)–O(5)	1.917(4)	1.9492(16)	O(5)–Cu(1)–O(1)	176.42(18)	176.57(7)
Cu(1)–O(1)	1.928(4)	1.9635(16)	O(5)–Cu(1)–N(3)	91.55(18)	91.74(8)
Cu(1)–N(3)	2.044(5)	2.073(2)	O(1)–Cu(1)–N(3)	91.29(18)	91.01(7)
Cu(1)–N(4)	2.047(5)	2.067(2)	O(5)–Cu(1)–N(4)	89.31(18)	89.34(8)
Cu(1)–N(5)	2.306(5)	2.317(2)	O(1)–Cu(1)–N(4)	88.41(18)	88.48(8)
O(1)–C(1)	1.289(7)	1.294(3)	N(3)–Cu(1)–N(4)	167.0(2)	166.21(8)
O(2)–C(1)	1.226(7)	1.233(3)	O(5)–Cu(1)–N(5)	86.77(18)	86.89(7)
O(5)–C(20)	1.265(6)	1.287(3)	O(1)–Cu(1)–N(5)	90.81(19)	90.82(7)
O(6)–C(20)	1.240(6)	1.249(3)	N(3)–Cu(1)–N(5)	95.04(19)	95.17(8)
C(1)–C(2)	1.527(8)	1.541(3)	N(4)–Cu(1)–N(5)	98.0(2)	98.61(8)
C(20)–C(21)	1.531(7)	1.531(3)	C(1)–O(1)–Cu(1)	122.6(4)	121.03(16)
N(3)–C(39)	1.323(7)	1.349(3)	C(20)–O(5)–Cu(1)	126.9(4)	125.39(15)
N(3)–C(43)	1.351(7)	1.355(3)	C(39)–N(3)–Cu(1)	124.1(5)	122.52(17)
N(4)–C(44)	1.342(7)	1.345(3)	C(43)–N(3)–Cu(1)	120.2(4)	120.35(17)
N(4)–C(48)	1.342(7)	1.350(3)	C(39)–N(3)–C(43)	115.7(6)	117.1(2)
N(5)–C(53)	1.336(7)	1.353(3)	C(44)–N(4)–Cu(1)	122.9(5)	122.08(18)
N(5)–C(49)	1.346(7)	1.355(3)	C(48)–N(4)–Cu(1)	121.3(5)	120.80(18)
			C(44)–N(4)–C(48)	115.5(6)	116.8(2)
			C(53)–N(5)–Cu(1)	121.8(5)	121.15(17)
			C(49)–N(5)–Cu(1)	122.2(4)	121.37(17)
			C(53)–N(5)–C(49)	115.9(6)	117.3(2)
			O(2)–C(1)–O(1)	124.7(6)	125.6(2)

			O(6)–C(20)–O(5)	125.4(5)	125.2(2)
			O(2) –C(1) –C(2)	120.3(6)	119.9(2)
			O(1)–C(1) –C(2)	115.0(6)	114.5(2)
			O(6)–(20)–C(21)	117.5(5)	118.8(2)
			O(5)–C(20)–C(21)	117.0(5)	116.1(2)
			τ	0.1570	0.1727

*Symmetry operation: (1) x, y, z; (2) -x, y+1/2, -z+1/2; (3) -x, -y, -z; (4) x, -y-1/2, z-1/2

Table 8. Selected bond lengths (Å) and bond angles (°) within Complex 2.

***Bond lengths* (Å)**		***Bond angles* (°)**	
Cu(1)–O(1)	1.9719(14)	O(1)–Cu(1)–O(1) *	180.0
Cu(1)···O(2)	2.5696(16)	O(1)– Cu(1)–N(2)	93.22(7)
Cu(1)–N(2)	2.051(2)	O(1)–Cu(1)–N(2)	86.78(7)
O(1)–C(1)	1.291(2)	N(2)–Cu(1)–N(2)*	180.0
O(2)–C(1)	1.232(2)	C(1)–O(1)–Cu(1)	103.37(13)
C(1)–C(2)	1.528(3)	O(2)–C(1)–O(1)	122.6(2)
N(2)–C(23)	1.488(3)	O(2)–C(1)–C(2)	122.27(19)
N(2)–C(20)	1.493(3)	O(1)–C(1)–C(2)	115.17(18

*Symmetry operation: (1) x, y, z (2) -x, -y, -z

Discussion

Synthesis

The donor strength of the solvent and the presence or absence of strong donor ligands in the solvent play an integral role in determining the nature of the coordination complexes containing carboxylate donors.[3,20,21,41] Both monomer and dimer Cu complexes can be formed for a given ligand of the formula L^1; depending upon the electronic properties of the solvent or ligands present in the solvent, as evident by the results reported here where complexes were formed with a bidentate carboxylate bridged Cu-Indo dimer, monodentate bis(carboxylato) Cu-Indo monomer (Complex

1) and unsymmetrical bis(bidentate) chelates in monomers such as Complex 2. The axial ligands can be exchanged with the solvent used for the recrystallisation procedure, or strong donor ligands present in the solvent used for the recrystallisation procedure, and this leads to changes in Cu coordination, such as observed in the preparations of Complex 1 and Complex 2 and further examples in the literature.[29,40,41] This is very important for designing pharmaceutical formulations since the solvents or the excipients used sometimes could lead to a change in the structure of Cu-Indo so potentially affecting biological activity, *e.g.*, toxicity.

In the synthesis of Cu-Indo complexes, the preference for monomer over dimer formation in Cu-Indo complexes correlates with the donor capacity of the axial ligands, with strong donors such as Py and Pyrro, preferring monomers.

UV–Vis spectroscopy

There is debate in the literature[2,28] as to whether the ε value of band I for some mononuclear and dinuclear Cu(II) complexes NSAIDs are similar. It was pointed out that the molar absorptivities for the monomeric pyridine analogues of the Cu(II) complexes of the NSAIDs naprosyn, $\varepsilon_{dmf} = 301\ M^{-1}\ cm^{-1}$, and ibuprofen, $\varepsilon_{dmf} = 263\ M^{-1}\ cm^{-1}$, [18,28] are similar to that of a dimeric DMSO Cu(II) complex of ibuprofen, $\varepsilon_{dmf} = 398\ M^{-1}\ cm^{-1}$.[18,28] Elsewhere, it has been pointed out that the value of the molar absorptivity for the dimeric DMSO Cu(II) complex of ibuprofen ($\varepsilon = 178\ M^{-1}\ cm^{-1}$) [25,28] is approximately half that for other dimeric Cu complexes. For the monomeric pyridine analogues of the Cu(II) complexes of the NSAIDs, naprosyn and ibuprofen, the solvent used to record the solution state UV–Vis spectra was DMF, which is different from the solvent ligand, pyridine. Obviously, ligand-exchange reactions can occur with the solvent that could lead to structural changes, which would be reflected in the UV-Vis spectra.[18] Values have been reported for the molar absorptivity for the dimeric DMSO Cu(II) complexes of naprosyn ($\varepsilon_{DMSO} = 457\ M^{-1}\ cm^{-1}$) and ibuprofen, $\varepsilon_{DMSO} = (380\ M^{-1}\ cm^{-1})$ in DMSO as the solvent and the monomeric pyridine Cu(II) complexes of naprosyn ($\varepsilon_{Py} = 85\ M^{-1}\ cm^{-1}$) and ibuprofen, ($\varepsilon_{Py} = 66\ M^{-1}\ cm^{-1}$)[18] in Py as the solvent. There is conflict in the ε values reported in 1990[25] and 1992[18] papers with the same author for the dimeric

DMSO Cu(II) complex of ibuprofen, which was later reported as 380 M^{-1} cm^{-1}.[18] Overall, it is clear that the intensities, ε values, of band I in the solution-state UV-Vis spectra are much higher for dinuclear carboxylate complexes than for mononuclear complexes, which can be used to determine the presence of monomeric or dimeric units. Moreover, the position of band I can be used to distinguish between the five-coordinate complexes with monodentate ligands (e.g., Complex 1) and tetragonally distorted octahedral complexes containing unsymmetric chelating Indo ligands, such as Complex 2.

Vibrational spectra

Characterisation of $[Cu_2(Indo)_4L_2]$ (L = DMA, ACN, THF), $[Cu(Indo)_2(Py)_3]$ and $[Cu(Indo)_2(Pyrro)_2]$ using solid-state FT IR spectroscopy also allowed the coordination mode of the carboxylate ligands to be distinguished from the shifts in the bands due to the $\nu_{asym}C(=O)_2$ stretches and the loss of the bands due to the ν_{carbo}(O–H) stretches of IndoH. The shift in wavenumbers of the $\nu_{sym}C(=O)_2$ bands is different between dimeric bridging and monomeric unidentate coordination. All of the $\Delta\nu$ values are ca. 200-220 cm^{-1} for bridging $[Cu_2(Indo)_4(L)_2]$, which are greater than for those for unidentate coordination in $[Cu(Indo)_2(Py)_3]$ (178 cm^{-1}), which is consistent with reports in the literature on related complexes.[2,21] However, the $\nu_{sym}C(=O)_2$ stretches that occur at lower frequencies of around 1400 cm^{-1} and ~1440 cm^{-1} in the dimeric and monomeric complexes, respectively, are in the IR fingerprint region, where they overlap with other bands from the Indo ligand, the solvent ligand and uncoordinated solvent molecules of crystallisation, which make correct assignment of $\nu_{sym}C(=O)_2$ difficult and less certain. For example, the stretching vibrations for the pyridine ring ($\nu C=C$ and $\nu C=N$) occur in the region between 1600–1430 cm^{-1}, which could overlap with the $\nu_{sym}C(=O)_2$ band at 1445 cm^{-1}. Solid-state IR spectra of the complexes were useful in revealing the presence of solvent stretching vibrations, such as those of DMA (ν_{amide}(C=O) at 1654 cm^{-1}) and ACN ($\nu_{C\equiv N}$ at 2363, 2335 and 2277 cm^{-1}), but this does not show that the solvent molecules are coordinated to the Cu centre.

EPR spectroscopy

The EPR spectra of the Indo complexes are diagnostic for distinguishing between monomers and dimers in both solution and the solid state.[2,21,23,29,38] The results reported here also show the value of the EPR spectroscopy in determining the structure of the monomers, as distinctively different EPR spectra are obtained from the Py and Pyrro complexes due to their different symmetries.

X-ray Powder Diffraction

Examination of these patterns shows very distinct differences between monomer and dimer structures, which are again diagnostic. They also show that the bulk material is the same as that used to determine the single-crystal pattern.

Structural Trends

It is uncommon to have present a series of dimeric Cu(II) complexes with the same carboxylate bridging ligand where the apical ligand is changed over a range of the *O*- and *N*-donor capacities. This range also provides the first illustration of a comparison of the effects of axial ligands in dimeric Cu complexes with the relatively weak *O*- and *N*-donor capacity ligands, THF and ACN, and strong *O*- and *N*-donor ligands. The strength of donor capacity (acceptor number) is as follows:[16,17]

ACN < THF < DMF < DMA < Py

Although the donor number of Pyrro does not appear to have been reported, it is also expected to be a strong donor ligand by analogy with other similar *N*-donor ligands. There are clear trends in the Cu–Cu distance and the Cu displacement from plane that reflects the donor capacity of the axial ligand.[1] The weakening of the Cu–Cu bond with increasing donor capacity of the solvent explains why monomers are formed with *N*-donor solvents that are strong donor solvents and it is likely that these solvents in general will result in such complexes.

The carboxylate groups of both of the mononuclear complexes, Complex 1 and Complex 2, reveal the correlation[46] of an increase in the length of the bound carboxylate arm C–O(1), which is accompanied by a decrease in the length of the unbound or weakly bound arm C–O(2). Compared to dinuclear Cu-Indo complexes,

there are no significant differences in the Cu–O(Ac) bond length, however, the C–$O(Ac)_{av}$ bond length in the dinuclear Cu-Indo complexes are shorter than the bound carboxylate arm C–O(1) and somewhat longer than the unbound or weakly bound arm C–O(2) in both mononuclear Cu-Indo complexes, Complex 1 and Complex 2. This is a consequence of delocalisation between the two C–O bonds in the dinuclear Cu-Indo complexes. Such differences account for the different shifts observed in the carboxylate stretching frequencies between the mononuclear and the dinuclear Cu-Indo complexes in their IR spectra.

Importantly the carboxylate electron delocalisation stabilised the dinuclear bridged Cu-Indo complexes compared with monodentate binding in $[Cu(Indo)_2(Py)_3]$ (the Indo ligand was much more weakly bound in $[Cu(Indo)_2(Py)_3]$). Although the mononuclear complex, $[Cu(Indo)_2(Pyrro)_2]$, exhibited only weak off axis secondary coordination from the second 'carbonyl' oxygen of the carboxylate, these two weak Cu···O(2) interactions exert a crucial and significant effect for the stabilisation of this complex to ligand substitution, which is reflected in the gastrointestinal toxicity studies (Example 2).

Example 2 - Efficacy and Safety in Rats: A Comparison of Different Pharmaceutical Formulations

This example compares the efficacy and safety of a complex of formula (1), bis(η^2-*O*,*O*'-Indo)bis(pyrrolidine)copper(II), $[Cu(Indo)_2(Pyrro)_2]$ (Complex 2), the dimer complex, $[Cu_2(Indo)_4(DMF)_2]$, and the monomer $[Cu(Indo)_2(Py)_3]$ (Complex 1) in a series of *in vivo* studies for the assessment of the complexes as anti-inflammatory agents and for their ability to induce acute gastrointestinal ulceration.

Animals. Sprague-Dawley rats weighing 200-250 g were housed in metabolic cages four days before study and allowed free access to standard laboratory rat chow (Purina Rat Chow, Ralston Purina, St Louis MO, USA) and tap water. Animals were supplied by the laboratory animal services at the University of Sydney and housed in the Bosch animal house facility of the University of Sydney at ambient temperature and

humidity with a 12-h light-dark cycle. The experimental animal protocols were approved by the Animal Ethics Committee of the University of Sydney in July 1999 and updated in May 2002, approval number L24/7-99/3/2972 and L07-1/2004/3/3846.

Chemicals. IndoH, carboxymethylcellulose (CMC) and carrageenan Type 1 were purchased from Sigma Aldrich. Technical grade formaldehyde was purchased from Ajax Chemicals (Auburn, Australia).

Dosing Forms and Administration. Rats were orally dosed *via* a curved feeding needle (Harvard Apparatus) attached to a 1-mL syringe. IndoH or an equimolar indomethacin dose of the test compound ($[Cu_2(Indo)_4(DMF)_2]$, $[Cu(Indo)_2(Py)_3]$ or $[Cu(Indo)_2(Pyrro)_2]$) suspended in 0.5 mL of 2% (w/v) CMC solution were used in the treatments. The dose of each compound is listed in Table 9.

Table 9. Dose of each compound in the animal tests

Compound	Equimolar Indo Dose (mg/kg)
IndoH	10.00
$[Cu_2(Indo)_4(DMF)_2]$	11.90
$[Cu(Indo)_2(Py)_3]$	14.17
$[Cu(Indo)_2(Pyrro)_2]$	12.86

Inhibition of Carrageenan-Induced Paw Edema (anti-inflammatory activity of the test compounds): The control cohort was dosed solely with CMC (2%) solution. Inflammation was induced one hour after dosing with the NSAID (or vehicle), by injecting with carrageenan (0.1 mL, 2% w/v in isotonic saline) into the plantar region of the hind paw ($n = 3$) (Winter, C. A.; Flataker, L., *Pharmacol. Exp. Ther.* **1965**, *150*, 165-171). The thickness of the paw was measured at the ventral dorsal footpad using digital callipers prior to dosing and at 3 and 5 h after carrageenan injection. Paw volume was measured prior to dosing and at 3 and 5 h after carrageenan injection by submerging the right hind paw in water up to an ink mark on the skin over the lateral

malleus.[4] The vessel containing the water was tared to zero on a top pan balance and the volume of fluid displaced was measured directly as a positive force (in grams). As the density of water is 1 g mL^{-1}, a measurement of 1 g corresponds to a volume of 1 mL. The mean percent edema or percent inhibition of edema was determined as:

$$\% \text{ edema} = \left[\frac{\text{volume of inflamed paw - volume of paw prior to dosing}}{\text{volume of paw prior to dosing}}\right] \times 100 \quad \text{I}$$

$$\% \text{ inhibition} = \left[\frac{\% \text{ edema (control)} - \% \text{ edema (drug)}}{\% \text{ edema (control)}}\right] \times 100 \quad \text{II}$$

The results are shown in Figure 9.

Acute Macroscopic Gastric Damage.

Method one: Rats were fasted with access to water for 24 h prior to dosing and 3 hours post dosing. Each group of rats (n = 3–6 per group) was orally dosed with IndoH, or an equimolar IndoH dose of test compound listed in Table 9, or vehicle. Three hours after administration of the test compound, the rats were euthanased and the stomach was excised and opened by incision along the greater curvature. The stomach was rinsed, submerged in 10% formaldehyde for 1 h and the extent of macroscopic gastric toxicity was examined, which is expressed as the summation of the area of macroscopic ulcerations (mm^2).

Method two: After the aforementioned anti-inflammatory activity experiments, the rats were immediately euthanased. Similarly, the stomach was excised and opened by incision along the greater curvature for the examination of the macroscopic ulcerations (mm^2).

Since there were no significant differences in the results obtained by the two methods, the results shown in Figure 8(1) are those of the two methods combined.

Small Intestinal Macroscopic Damage. Rats were allowed free access to food and water throughout and prior to the assay period. Each group of rats (n = 3–6 per group) was orally dosed with IndoH, or an equimolar IndoH dose of test compound listed in

Table 9, or vehicle. At 24 h after dosing, rats were euthanased and the entire small intestine was excised and flushed with water to expel the intestinal contents and opened along the anti-mesenteric side. The intestine was examined from 10 cm distal to the ligament of Treitz to the ileocecal junction for macroscopic ulcerations. The degree of ulcerations is expressed as the summation of the area of macroscopic ulcerations (mm^2).

Statistical analysis: All inhibition of carrageenan-induced paw edema and gastrointestinal ulceration data are expressed as the standard error of the mean (±sem). Comparisons among the control and treatment groups were made using one-way analysis of variance followed by a Student-Newman-Keuls *t*-test using the GraphPad Instat statistical program. With all analyses, an associated probability (*P* value) of less than 5% ($P < 0.05$) was considered significant. The calculation of the power of the experiment to compare two treatment groups with a *P*-value threshold of 0.05 was determined using the GraphPad StatMate program (*GraphPad Instat*; version 3.01 for WIN95/NT, GraphPad Software Inc., 1998).

Results

Acute Macroscopic Gastric Damage. Figure 8(1) shows the results of the macroscopic gastric ulcerations induced by IndoH and equimolar Indo dose of test compounds in 2% (w/v) CMC solution. $[Cu_2(Indo)_4(DMF)_2]$ and $[Cu(Indo)_2(Pyrro)_2]$ show significant reductions ($P < 0.01$) in gastric ulcerations as compared to those induced by IndoH and a physical mixture of IndoH and Cu-acetate. $[Cu(Indo)_2(Pyrro)_2]$ also exhibited a significant reduction in gastric ulceration compared with $[Cu_2(Indo)_4(DMF)_2]$. There is no significant difference in the gastric ulcerations induced by $[Cu(Indo)_2(Py)_3]$ or IndoH. Interestingly, gastric damage was significantly increased in rats treated with a physical mixture of IndoH and Cu-acetate compared with rats treated with the IndoH alone. Similar trends were observed in the small intestine ulcerations (Figure 8(2)).

In a second experiment, using a different sample of $[Cu(Indo)_2(Pyrro)_2]$ that was precipitated from solution with diethyl ether, the average gastric ulceration for four rats was higher at 21 mm^2, which is the same, within experimental error, as was

observed for $[Cu_2(Indo)_4(DMF)_2]$ at the same dose of Indo. The efficacy was also similar to $[Cu_2(Indo)_4(DMF)_2]$.

Small Intestinal Ulceration. The results (Figure 8(2)) show that $[Cu(Indo)_2(Pyrro)_2]$ has a similar low small intestinal toxicity as is observed for $[Cu_2(Indo)_4(DMF)_2]$, but $[Cu(Indo)_2(Py)_3]$ has a significantly higher toxicity (Figure 8(2)).

Efficacy of the New Complexes. Figure 9 shows that Complex 1 is as effective as $[Cu_2(Indo)_4(DMF)_2]$ in reducing inflammation. $[Cu_2(Indo)_4(DMF)_2]$ is currently used in certain veterinary applications.

Discussion

The results establish that the mononuclear complex of formula (1) has comparable efficacy as the Cu-Indo dimers currently used in veterinary applications, and surprisingly causes similar or less ulceration in the stomach and somewhat less ulceration in the small intestine than the dimer. In contrast, the monomer of the formula (2) caused more ulceration in the stomach and small intestine than the dimer.

In the claims that follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

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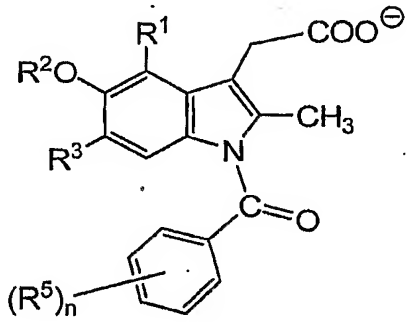
CLAIMS:

1. A complex of the formula (1):

$[Cu(\eta^2\text{-}L^1)_2L_2]^p$ (1)

wherein "η^2-L^1" is a bidentate ligand of the formula L^1:

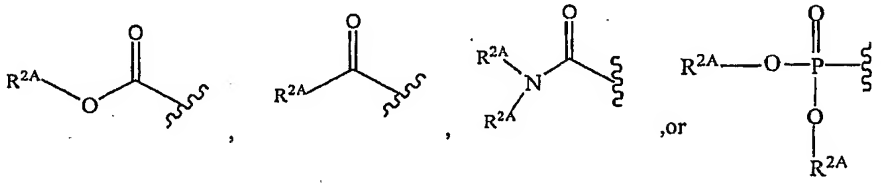


(L^1)

wherein:

R^1 is H or halo;

R^2 is H; a C_1 to C_6 alkyl, an alkenyl or an alkynyl, where the C_1 to C_6 alkyl, alkenyl or alkynyl may be optionally substituted; or



wherein each R^{2A} is independently selected from the group consisting of H, C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl and arylalkyl; where the C_1 to C_6 alkyl, alkenyl, alkynyl, aryl, cycloalkyl or arylalkyl may be optionally substituted;

R^3 is H or halo;

each R^5 is independently selected from the group consisting of halo, $-CH_3$, -CN, $-OCH_3$, $-SCH_3$ and $-CH_2CH_3$, where the $-CH_3$, $-OCH_3$, $-SCH_3$ or $-CH_2CH_3$ may be optionally substituted; and

n is 1, 2, 3, 4 or 5;

each L is independently selected and is a monodentate ligand,

and p is the charge of the complex.

2. A complex according to claim 1, wherein each R^5 is a halo substituent.

3. A complex according to claim 2, wherein n is 1, 2 or 3 and each R^5 is independently selected from Cl and Br.

4. A complex according to any one of claims 1 to 3, wherein L^1 is the anion of indomethacin.

5. A complex according to any one of claims 1 to 4, wherein L is a ligand containing an *N*-heterocyclic group.

6. A complex according to any one of claims 1 to 4, wherein L is pyrrolidine or imidazole.

7. A pharmaceutical composition comprising a complex according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

8. A composition according to claim 7, wherein the composition is suitable for oral, rectal, nasal, topical, ophthalmological, vaginal or parenteral administration.

9. A composition according to claim 8, wherein the composition is suitable for oral administration.

10. A method of treating an inflammatory condition in a human or animal, the method comprising administrating to the human or animal a therapeutically effective amount of a complex according to any one of claims 1 to 6.

11. A method according to claim 9, wherein the animal is a dog, a cat, a cow, a horse, or a camel.

12. A method according to claim 10 or 11, wherein the complex is administered

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orally, rectally, by nasal spray, topically, ophthalmologically, vaginally or parenterally.

13. A method according to claim 12, wherein the complex is administered orally.

14. Use of a complex of any one of claims 1 to 6 in the manufacture of a medicament for the treatment of an inflammatory condition.

FIGURE 1

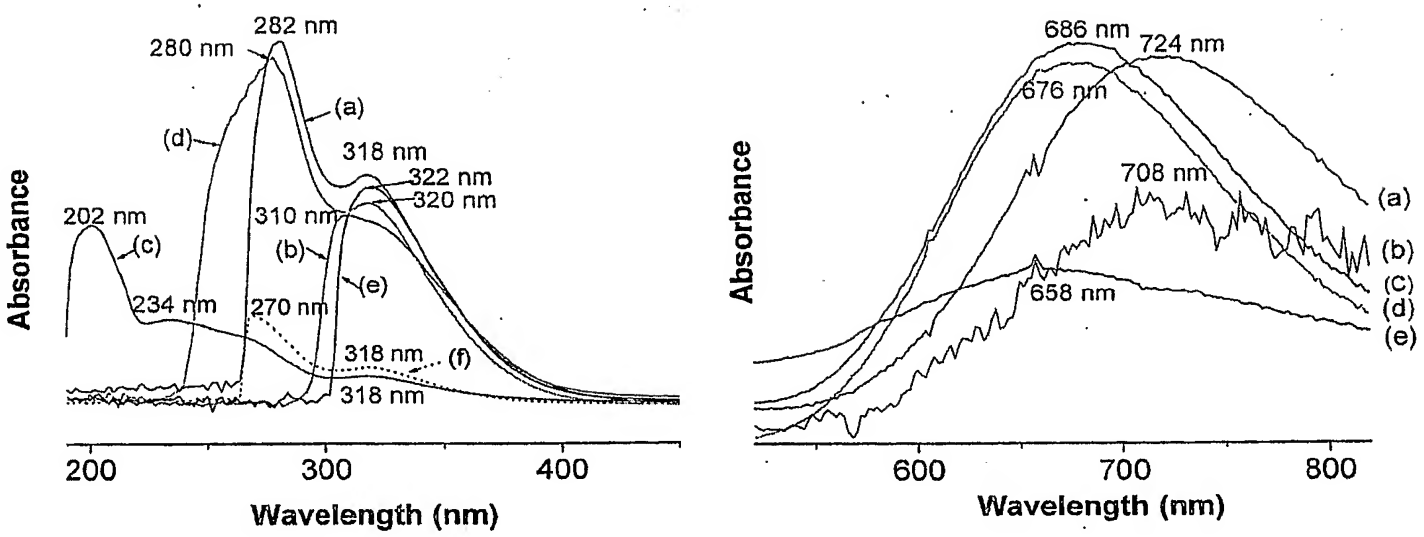
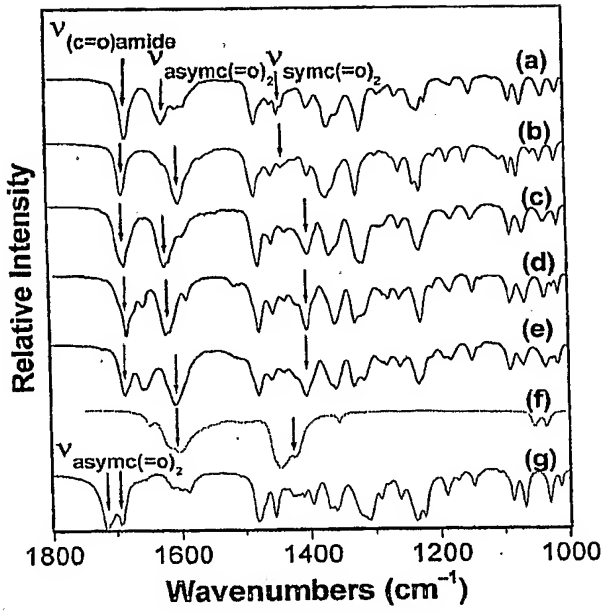


FIGURE 2



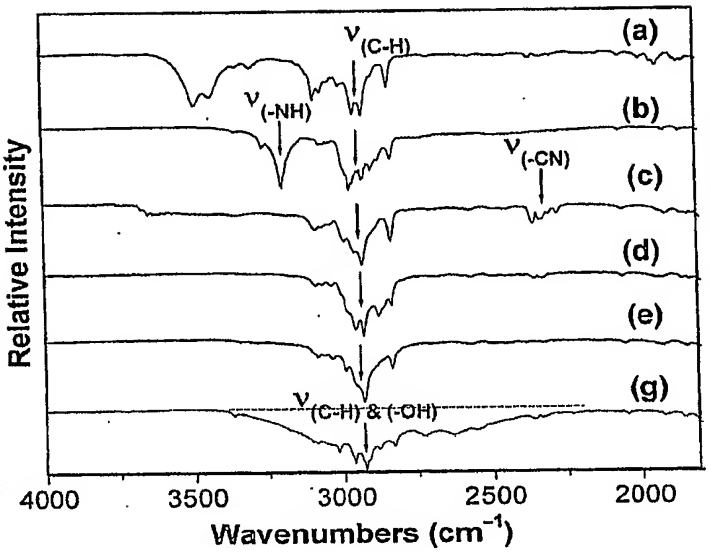


FIGURE 3

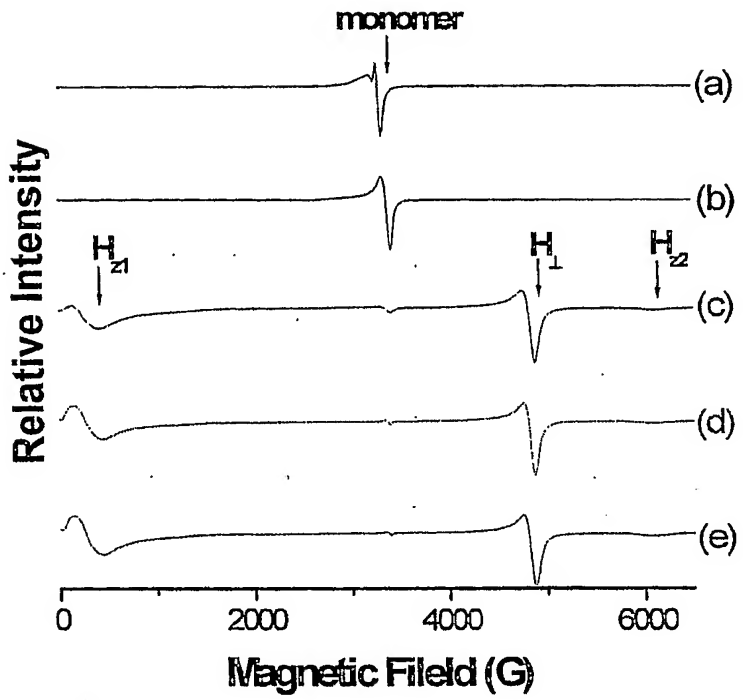
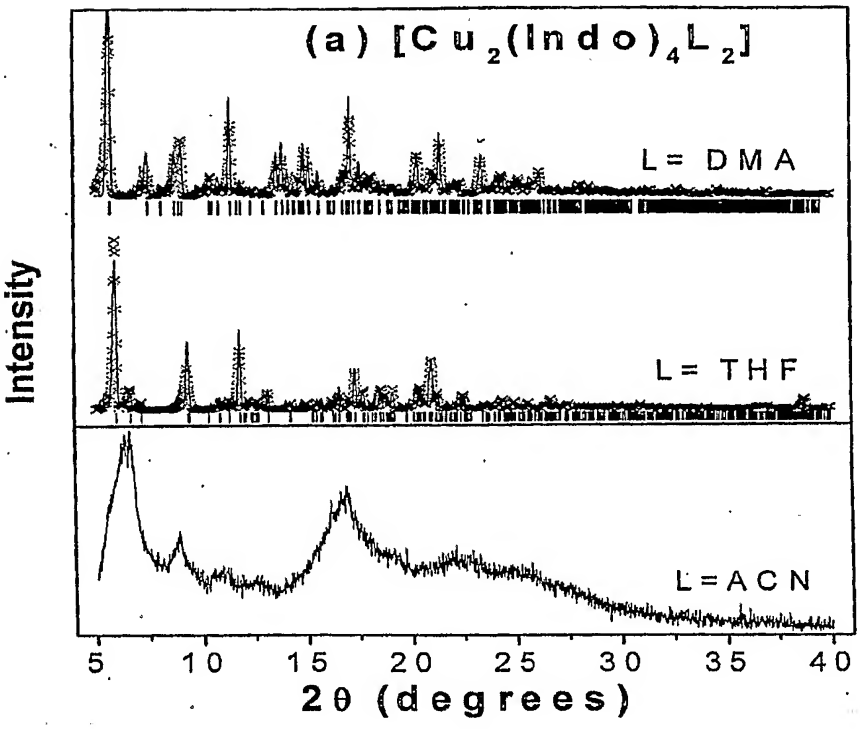


FIGURE 4



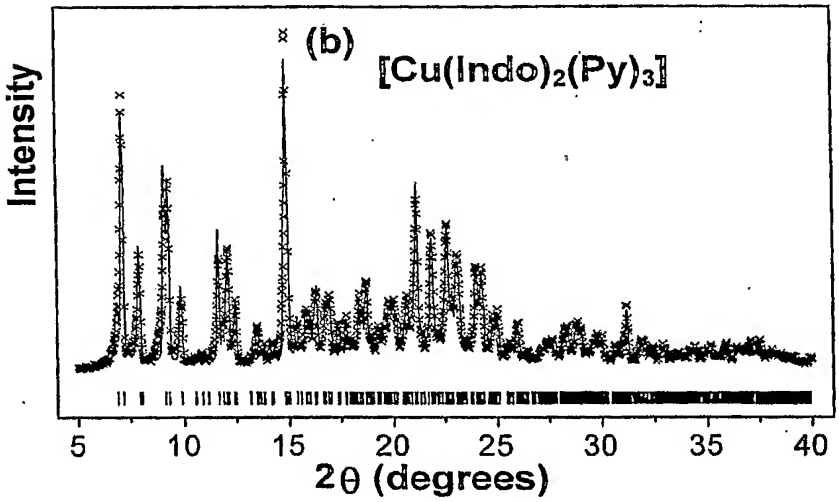
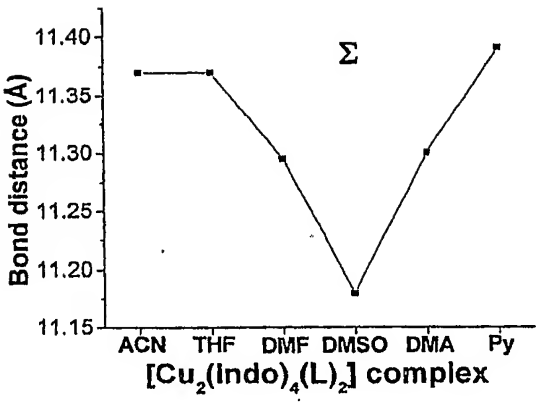
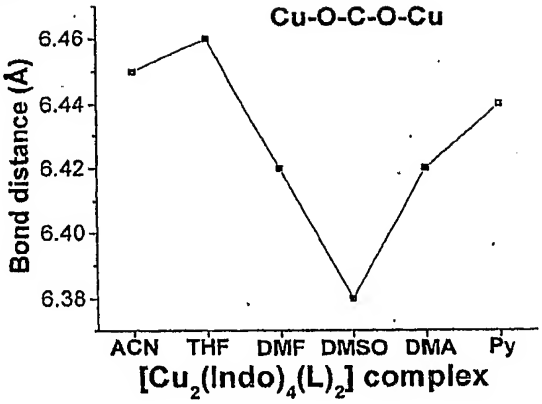
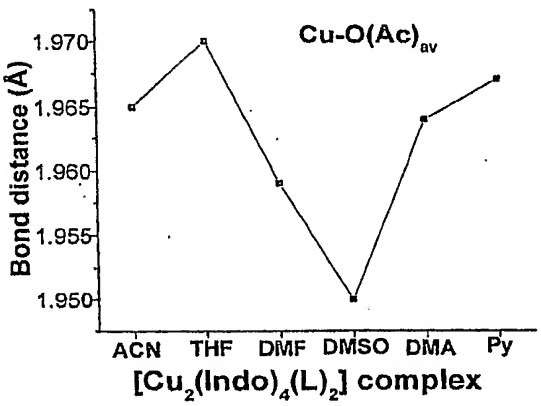
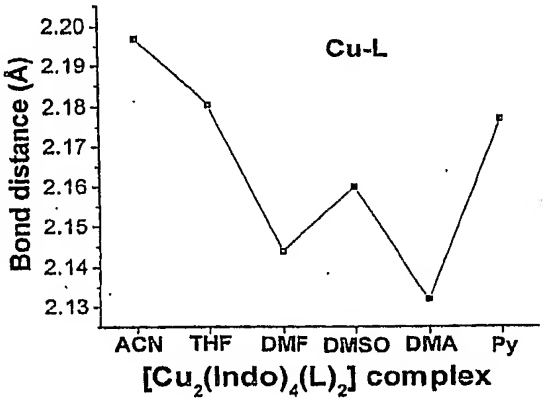


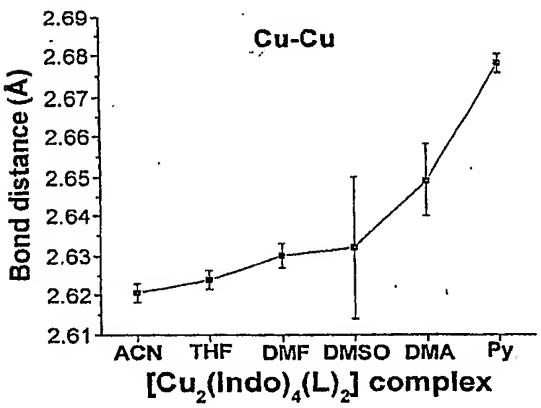
FIGURE 5

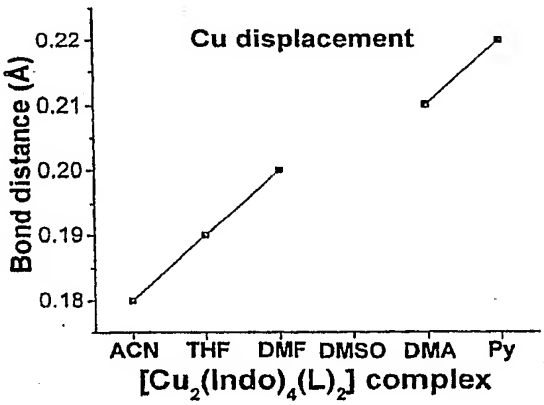












Solvent	ACN	THF	DMF	DMA	DMSO	Py
Donor number D_N	14.1	20.0	26.6	27.8	29.8	33.1

FIGURE 6

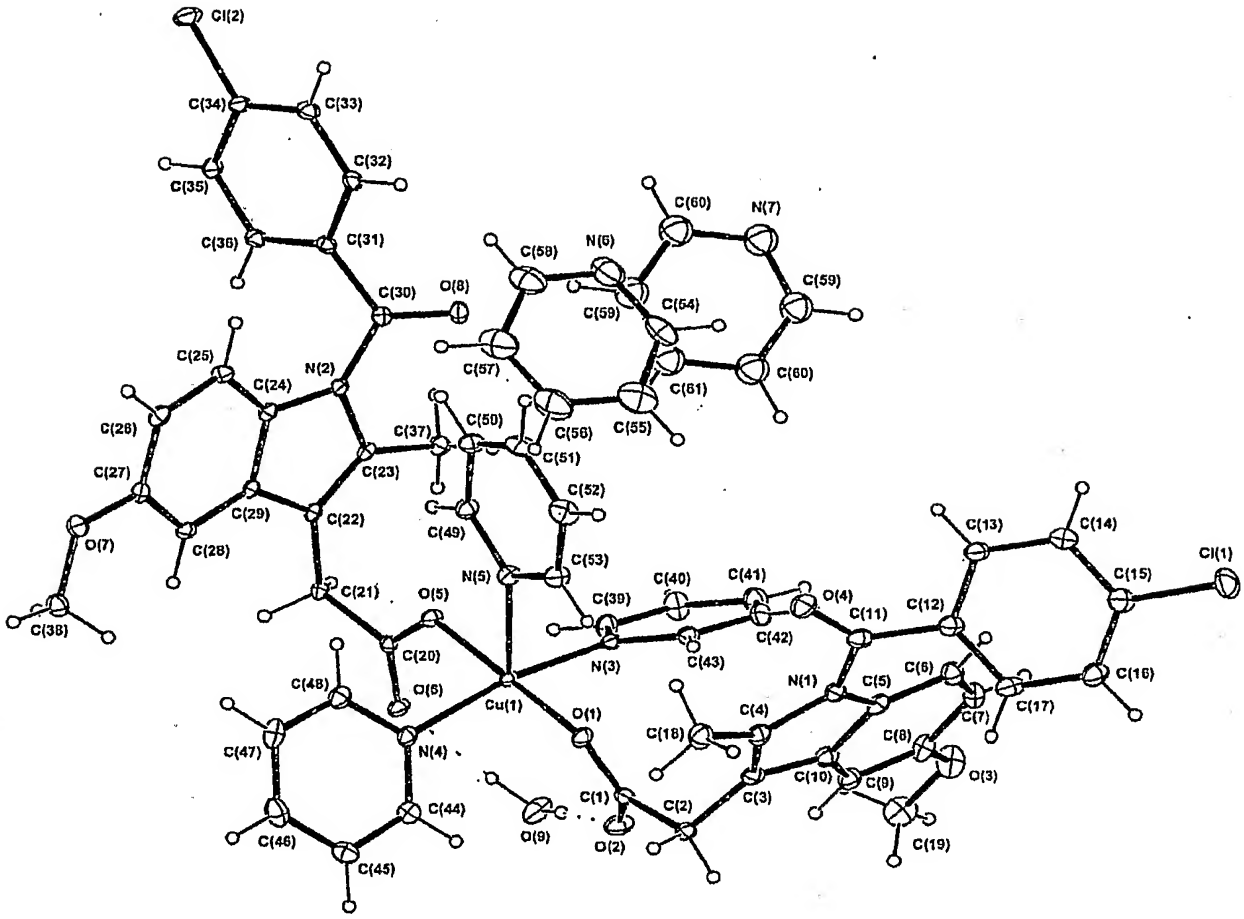


FIGURE 7

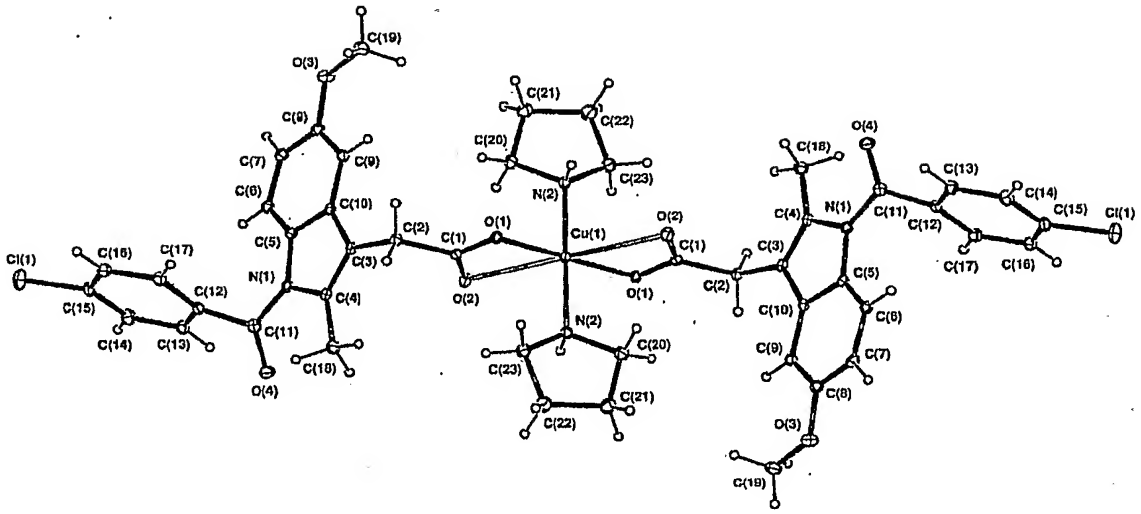
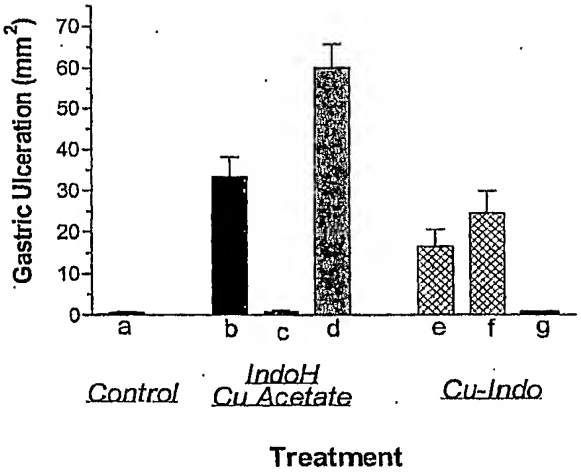


FIGURE 8

(1)



(2)

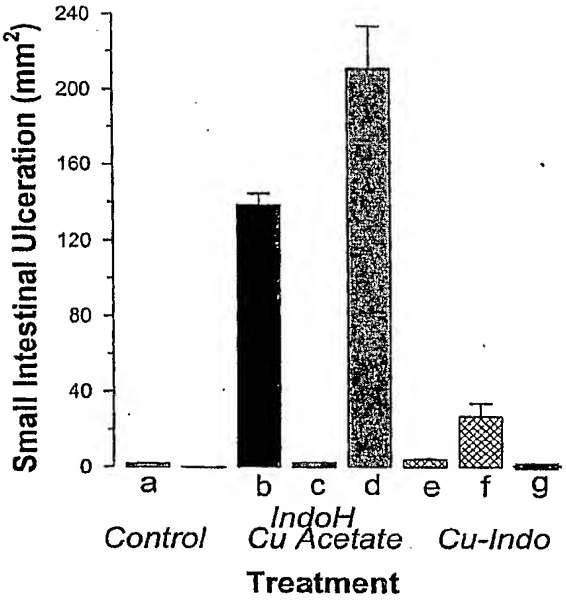


FIGURE 9